Evidence For Using Immunosuppressive Treatments When Treating Idiopathic Non-Infectious Uveitis: A Systematic Review and Meta-Analysis

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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(Thesis format: Monograph)

by

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Graduate Program in Epidemiology and Biostatistics

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Abstract

Idiopathic non-infectious uveitis is the spontaneous inflammation of the eye, which can lead to blindness if not treated correctly. Due to long-term side effects of corticosteroids, 4 classes of off-label immunosuppressive treatments are sometimes used (alkylating agents, inhibitors of T-lymphocyte signalling, antimetabolites and biological modifiers). We conducted a systematic review and meta-analysis to assess the effectiveness of 3 treatment classes on uveitis patients with similar characteristics. Results of the systematic review concurred with the conclusions from the meta-analysis, which found that all immunosuppressive treatments improved patient vision, with a statistically significant change in logMAR of -0.11 (95% CI of -0.152 to -0.061, p=0). The subgroup analysis found antimetabolites and T-cell inhibitors improved patient vision which was statistically significant, with antimetabolites showing a better change in logMAR of -0.131 (95% CI -0.211 to -0.050, p=0.001. $I^2=0\%$). These findings could inform policy and help develop concrete guidelines for treating uveitis patients.

Keywords

Idiopathic Uveitis, Anterior, Posterior, Intermediate, Immunosuppressive treatment, Alkylating agents, Inhibitors of T-lymphocyte signaling, Antimetabolites, Visual Acuity, LogMAR, random effects, raw mean difference, meta-analysis, subgroup analysis, meta-regression
Co-Authorship Statement

The work presented herein was performed solely by the author. As stated in Chapter 5, the only exception was the literature search and level 1&2 screening. The search strategy and literature search was done with the help of Lorraine Leff, who was the librarian on my project. Also, for level 1 screening Andrea Coronado (AC) was the other reviewer alongside myself (HS). For level 2 screening the second reviewer was Shruti Sharma (SS) and I was the first reviewer. Discrepancies between any of the screenings were dealt with Dr. Hodge.
Dedication and Acknowledgments

I would like to acknowledge the department of Epidemiology and Biostatistics for providing me with an excellent educational experience. The courses and material helped a great deal with my understanding of epidemiology.

I would also like to acknowledge all the help and support I received from Dr. William Hodge and Dr. Monali Malvankar. They provided me with valuable advice and enhanced my understanding and knowledge on how to conduct a meta-analysis and general aspects relating to epidemiology.

Dedicated to my loving family for their support through both the good and bad times. Special thanks to my brother, Balgurinder Singh, for his motivation and support he provided to keep me moving forward.
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List of Abbreviations

AZA- Azathioprine

COS- Canadian Ophthalmology Society

CSA- Cyclosporine

CUS- Canadian Uveitis Society

IMM- Immunosuppressives

I-V- Fixed effects model (for forest plot)

JIA- Juvenile idiopathic arthritis

LogMAR- The Logarithm of the Minimum Angle of Resolution

L+D- Random effects model (for forest plot)

MMF- Mycophenolate Mofetil

MTX- Methotrexate

SD – Standard Deviation

SMD- Standardized Mean Difference

SUN- Standardization of Uveitis Nomenclature

TAC or FK-506- Tacrolimus

RCT- Randomized Controlled Trial

WMD- Weighted Mean Difference

VA- Visual Acuity
Chapter 1

1 Overview of Thesis and Introduction

1.1 Outline of Thesis

The primary objective of this thesis is to summarize the effects of the 3 immunosuppressive treatment groups used to treat idiopathic non-infectious uveitis patients. We conducted a systematic review and meta-analysis with studies that met our eligibility criteria. This chapter describes the terminology needed to understand what uveitis is, how it is treated and how the outcomes are measured for identifying whether treatments are effective or not. Then Chapter 2 discusses the literature for uveitis patients and gives a clear case as to why an evidence-based approach is required for this particular question, which leads into Chapter 3, justifications and objectives for the thesis. Before discussing the methods, Chapter 4 describes the concepts and terminology that is vital for describing and interpreting our meta-analysis. Chapter 5 outlines the methods used to reach our objectives, and Chapter 6 summarizes the results for the systematic review, quality assessment, meta-analysis, and publication bias analysis. Finally, Chapter 7 interprets the results and lists the strengths and limitations of the thesis, alongside possibilities for future research.

1.2 Introduction to Uveitis

Uveitis is inflammation of the eye, which can result in patients becoming blind if it is not treated correctly and it can affect both eyes (bilateral) or it can affect 1 of 2 eyes (unilateral). To understand how to treat uveitis patients, it is important to understand the anatomy of the eye as well as the mechanisms involved in the inflammation caused by uveitis. An article published in 2005 presented specific terms and guidelines used to define the various components of uveitis, which were updated from the 1987 International Uveitis Study Group (IUSG) that had developed criteria based mainly on anatomy. These terms were provided by uveitis specialists whose purpose was to develop international consensus for the use of terms associated with uveitis in the literature. The phrase coined for the use of these terms was the Standardization of Uveitis
Nomenclature (SUN). Two important classifications key to understanding how to treat uveitis patients were developed for the progression of the disease and the anatomy of the eye. A patient with uveitis may experience, acute, recurrent or chronic uveitis. Table 1 defines each course of disease.

**Table 1: Course of Disease**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Episode characterized by sudden onset and limited duration</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Repeated episodes separated by periods of inactivity without treatment ≥ 3 months in duration</td>
</tr>
<tr>
<td>Chronic</td>
<td>Persistent uveitis with relapse in &lt;3 months after discontinuing treatment</td>
</tr>
</tbody>
</table>

1.2.1 Anatomy

The progression of uveitis can also be associated with the location of the disease within the eye. Thus, the 2005 SUN guidelines and the 2007 European classifications anatomically classified locations within the eye as posterior, anterior or intermediate. The anatomical location of uveitis is one of the most important clues to the pathogenesis and treatment that a patient should receive.

**Figure 1: Anatomy of the eye and location of Uveitis**

1.2.1.1 Anterior Uveitis

Anterior uveitis involves the anterior chamber, which consists of all structures anterior to the iris, as indicated by the purple box in Figure 1. Usually, it is acute in nature and only 1 of the 2 eyes is usually affected (unilateral). About 67% to 90% of patients with uveitis have anterior uveitis. These patients are easier to treat than patients with uveitis in other locations. The most common symptoms exhibited by patients with anterior uveitis are dull pain in the eye, redness of the eye, blurred vision and photophobia.

1.2.1.2 Intermediate Uveitis

As shown in the Figure 1, the yellow box contains intermediate uveitis, which involves the area where the retina meets the anterior structures of the eye, that is, the pars plana and ciliary body. Intermediate uveitis is the least common type of uveitis, accounting for only 7-15% of cases. Both eyes are usually affected in patients with intermediate uveitis, and patients are more likely to have chronic inflammation. Furthermore, patients with intermediate uveitis commonly experience floaters and may experience painless blurred vision.

1.2.1.3 Posterior Uveitis and Panuveitis

Posterior uveitis involves the retina and choroid, which can be seen in Figure 1 surrounded with an orange box. It is seen in 15-22% of uveitis patients. Generally, it is chronic, recurrent and can affect both eyes. The underlying cause is often the result of an abnormal immune disease. That is, immune cells enter the eye and become active because they detect tissue that they identify as foreign or a threat to the individual. This creates a complex immune response that causes inflammation in the eye. Treating patients with autoimmune or idiopathic uveitis becomes difficult because it is hard to detect the cause of uveitis in these patients, and thus treatment varies between ophthalmologists. Posterior uveitis commonly causes blurred vision, floaters, and in some cases, severe visual loss. Some patients develop scotomata, which are small regions of less sensitive or absent vision.
Inflammation affecting the entire uvea is called panuveitis. People with panuveitis may be more likely to experience vision loss from the condition. Symptoms for patients with panuveitis include floaters, blurred vision or loss of vision. Generally these patients are considered idiopathic in nature, due to their cause being unknown and affecting the entire eye.

1.2.2 Etiology

In addition to the anatomy of the eye, uveitis is also differentiated by the etiology. Up to 50% of cases have underlying causes that are usually inflammatory (eg, Sarcoidosis), however there are some causes that are non-inflammatory (eg, syphilis, tuberculosis, and toxoplasmosis). The other 50% of cases do not have a cause are deemed as idiopathic, but the general consensus is that those are autoimmune cases without a simple category. The diagnosis for idiopathic uveitis is done by checking patients for the known causes of uveitis, if the workup comes back negative then they are considered idiopathic.

1.2.3 Epidemiology

Even though uveitis is a rare disease, it is still an important cause of blindness. The prevalence of uveitis is estimated to be about 115-204/100,000 persons. Uveitis is the cause of 30,000 new cases of legal blindness every year in the USA, and nearly 10% of visual loss in the Western world.

1.2.4 Age Range

Uveitis can affect any age group, from infants and children (juvenile idiopathic arthritis) to young adults (pars planitis and seronegative arthropathies) to the middle-aged (sarcoidosis and idiopathic) to the elderly (masquerade syndromes and idiopathic).

1.2.5 Final Remarks

The introduction of the SUN classification in 2005 has made it easier to diagnose patients with uveitis. Classification by progression, anatomy and/or cause of disease can facilitate diagnosis and treatment. For example, infectious uveitis, like herpes simplex viruses,
primarily causes acute or chronic anterior uveitis, and is easy to treat. However, the subset of idiopathic uveitis (spontaneous cause) is much harder to treat.

### 1.3 Treatments Administered to Uveitis Patients

Treatment depends on the location of the condition, severity, rate of recurrence and etiology. For single episode anterior uveitis, the use of topical corticosteroid preparations usually result in successful treatment. For moderate amounts of inflammation involving the intermediate or posterior structures, periocular or even intraocular steroids can be used successfully. For severe inflammation of the posterior part of the eye, especially in bilateral cases, treatment usually involves systemic immunomodulation. These agents include oral corticosteroids, which can only be used in a limited role due to their side effects, which include osteoporosis and bone fractures, aseptic hip fractures, induced diabetes mellitus, personality changes, and metabolic abnormalities.

Idiopathic uveitis is more complex to treat since its cause is unknown. Treatment for idiopathic uveitis can vary from steroids to immunomodulators. There is still a lot of debate regarding what treatment should be used for patients with idiopathic uveitis. Since 1949, corticosteroids have been used to treat active inflammation of the eye. Steroids reduce the inflammatory infiltration. However, there are many side effects from the use of steroids. This has led to advances in the methods by which steroids are administered, which has helped to lower the side effects. For example, periocular route administration (ie, injection around the eye), has reduced side effects since the steroid’s use is limited to the inflamed area. The ophthalmologist must be comfortable and the injection must be given accurately. In general, steroids are usually administered in high doses to patients that have acute uveitis. However, with chronic uveitis, high doses of steroids over a long period of time can cause severe side effects in patients, thus immunomodulators, such as alkylation agents (eg, cyclophosphamide), Inhibitors of T-lymphocyte signaling (eg, cyclosporine), antimetabolites (eg, azathioprine) and biological modifiers (eg, TNF-alpha) are more commonly used. For the purposes of this thesis we will not be
discussing biologics, but they are a new but more expensive way of dealing with uveitis patients.

A brief summary of each treatment group is given below.

1.3.1 Corticosteroids (First Line of Action in Uveitis Therapy)

Corticosteroids have been used since the 1950s. They work on multiple signaling mechanisms to inhibit inflammation, but have many adverse effects.\textsuperscript{19,20} Ocular side effects include cataract and glaucoma. The steroid dosage for vision threatening uveitis typically starts at 1mg/kg.\textsuperscript{22} This is the first line of treatment given to patients since it can quickly dampen the immune system and aid patients in recovering from acute, mild or moderate uveitis. However, steroids are generally only used for 1 to 3 months, after which the dosage is tapered. Steroids are not continued for chronic uveitis patients, as long term steroid use has significant side effects, both on the eye and on the rest of the body (if taken orally).\textsuperscript{22}

1.3.2 Antimetabolites

Patients that continue to experience symptoms while on corticosteroids, or those who have taken steroids over a long period of time and exhibit adverse effects, are prescribed antimetabolites. Antimetabolites function by inhibiting nucleic acid synthesis, thereby hindering the process of DNA synthesis. There are 3 types of drugs included in the antimetabolite drug class.

1.3.2.1 Azathioprine (Imuran, Azasan)

Azathioprine (AZA) functions as a purine nucleoside analog (basically mimicking the structures of DNA and RNA building blocks), thus it interferes with the synthesis of RNA and DNA.\textsuperscript{23} Azathioprine is orally absorbed and the initial dose of AZA is 1mg/kg/day, up to a maximum dose of 2.5-4mg/kg/day.\textsuperscript{23-26} Nausea and vomiting are common adverse effects, especially at the beginning of treatment.\textsuperscript{24}
1.3.2.2 Methotrexate (Rheumatrex, Trexall)

Methotrexate (MTX) also interferes with DNA production. MTX was introduced first as treatment for neoplasm in 1958. It basically functions to reduce cell proliferation, causes death to T-cells, and changes the response of B-cells. MTX was first introduced as a treatment for ocular inflammation in 1965.\textsuperscript{27-37} MTX can be given orally, subcutaneously, intramuscularly or intravenously, and is usually well tolerated.\textsuperscript{35} The initial dose of MTX is 7.5-12.5 mg/week, and the maximum dosage usually given is 25 mg/week. The most common adverse effects include: increased liver enzymes, ulcerative stomatitis and low white blood cell count, which can lead to lethargy, infection, nausea, abdominal pain and acute pneumonitis.\textsuperscript{30-37}

1.3.2.3 Mycophenolate Mofetil (cellcept, Myfortic)

Mycophenolate Mofetil (MMF) inhibits the production of B and T cells by causing deletion of nucleotides important for DNA production.\textsuperscript{38-51} MMF is taken orally and has been known to help adults and children. MMF is usually given twice day at dosages beginning at 500mg, up to a maximum of 1.5 gm. Among the most common side effects of this drug are high blood sugar, increased blood cholesterol levels and gastrointestinal tract complications.

1.3.3 Inhibitors of T-lymphocyte Signalling (Calcineurin Inhibitors)

T-cell inhibitors, or calcineurin inhibitors, were originally developed for use in organ transplantation.\textsuperscript{16} They are a class of drugs that inhibit the replication and activation of immune cells by inhibiting calcineurin, which is important in the activation and maturation of immune cells. Drugs found in this class include Cyclosporine (CsA), Tacrolimus (Fk-506), and Sirolimus.

1.3.3.1 Cyclosporine, CsA (Gengraf, Neoral, and Sandimmune)

CsA is mostly used as a T-cell suppressant. CsA has an intricate process, but the end result is the inhibition of the proliferation and maturation of T-cells.\textsuperscript{52-58} CsA is mainly given orally, and the initial dose ranges from 2.5-5 mg/kg/day, up to a maximum dosage
of 10 mg/kg/day [10-12]. Adverse events of CsA consists of nephrotoxicity, neurotoxicity, hypertension and increases the risk of infections.\textsuperscript{55}

1.3.3.2 Tacrolimus, FK-506 (Prograf, Advagraf, Protopic)

FK-506 is similar to CsA, in that it inhibits certain molecules that are needed for immune cell production. FK-506 is usually given orally, and the initial dose ranges from 0.15-0.30 mg/kg/day, up to a maximum of about .30 mg/kg/day.\textsuperscript{59, 62} Side effects can be severe and include blurred vision, infection, cardiovascular damage, hypertension, and nephrotoxicity.\textsuperscript{59-64}

1.3.3.3 Sirolimus (Rapamune)

Sirolimus is similar in its effect to the other two drugs in this class. However, the side effects of Sirolimus are more severe, including lung toxicity and cancer development.\textsuperscript{65, 66}

1.3.4 Alkylating Agents

Alkylating agents were mainly developed for the treatment of cancer, but were later used in the treatment of rheumatologic diseases.\textsuperscript{67} Alkylating agents work by damaging DNA through alkylation, resulting in the inhibition of DNA production and cell death. These are commonly used if other treatments fail.\textsuperscript{67, 68}

1.3.4.1 Cyclophosphamide (Cytoxan, Endoxan, Cytoxan, Neosar, Procytox, and Revimmune)

Cyclophosphamide is derived from mustard gas. It alkylates one of the bases in DNA, which leads to suppression of the immune system. It is orally and hepatically metabolized in the liver. Initially, patients are given about 1-2 mg/kg/day, up to about 3 mg/kg/day.\textsuperscript{70} Adverse reactions include nausea and vomiting, bone marrow suppression, stomach ache, diarrhea, and lethargy.\textsuperscript{69-73} Fertile aged patients will lose their fertility and so these drugs are not used in patients under 40, unless there is no alternative.
1.3.4.2 Chlorambucil (Leukeran)

Chlorambucil was created in 1953 as a less toxic substitute for cyclophosphamide, which functions using a slightly different mechanism. Chlorambucil is orally administered at initial doses of 0.1mg/kg/day, to maximum of 0.2 mg/kg/day. Bone marrow suppression is the most commonly occurring side effect of chlorambucil.\(^{74-79}\)

1.3.5 Final Remarks on Treatments

In reviewing the various treatment groups, it becomes apparent that there are a number of treatments that one can administer to uveitis patients. However, because the treatments are given off-label there are no specific guidelines for the use of these treatments in uveitis patients.\(^5\) Originally, these treatments were given and prescribed primarily to patients with rheumatoid arthritis.\(^16\) Due to their immunosuppressive nature, they were eventually given to patients with uveitis, as the idiopathic cases were mainly autoimmune. Furthermore, the known side effects for immunosuppressive treatment are taken from studies on patients with rheumatoid arthritis instead of patients with uveitis.

In Canada, patients with idiopathic uveitis are referred to a uveitis specialist. These patients tend to have similar characteristics when they present with idiopathic uveitis. Knowing which treatment will be most effective should also be taken into consideration alongside the age, severity of disease, and location of disease. Therefore, this systematic review will compile the literature on the various types of immunosuppressive treatments and create an environment in which they can be compared amongst each other when used to treat a patient with idiopathic non-infectious uveitis.

1.4 Outcomes Measured for Uveitis Patients

Once the treatment has been administered, there are a few ways to measure the efficacy of the idiopathic uveitis treatment. These measures include inflammation grade, Visual Acuity (VA), steroid discontinuation rate, uveitis relapse rate, and the adverse events that patients may experience with the treatment. A brief summary of each measure is given below.
1.4.1 Anterior/Posterior Inflammation Grade

Figure 2 below shows a table from the 2005 SUN paper, which allows uveitis specialists to numerically quantify the severity of Uveitis.¹

![SUN classification for severity of uveitis](image)

**Figure 2: The SUN classification for severity of uveitis**

*Table taken from SUN classification for Uveitis (1)*

Severity of disease is measured by a grade that can range from no inflammation (ie, 0) to intense inflammation (ie, 4+). It is usually measured twice, before treatment and after treatment, to see if the treatment resulted in any difference in the severity.¹

Before SUN was established in 2005, there were at least 4 other major systems used to measure inflammation grade. These systems are similar to SUN, but some of the differences make it difficult to compare the systems to one another.¹ Thus, SUN was established in order to standardize the way the inflammation grade is measured, which allows studies to be compared with one another. However, some of the studies included in this thesis were conducted before SUN was introduced, which means their systems of measuring inflammation will have been less standardized. Also, there is no correlation or conversion that can be drawn between pre-SUN studies and post-SUN studies. Thus, it is
difficult to compare the inflammation grade data and standardized the data from studies using different scales, making it a less viable option to do a meta-analysis on.

1.4.2 Visual Acuity

Visual acuity (VA) describes the sharpness of vision, which is measured by the eye's ability to resolve and recognize letters of varying sizes, through a VA test chart. This estimate is an essential indicator of ocular health and is used to measure the effectiveness of treatment in studies.

In order to understand which measure of VA is best for mathematical and/or clinical settings, it is important to understand which VA test charts are used and how they compare. There are many variations of test charts used in the clinical setting when evaluating vision. But their variations have been adapted from mainly two chart designs, the Snellen chart design and the Bailey–Lovie chart design (also called logMAR charts).

The Snellen chart design has been around since 1862 and is still used to this day in a clinical setting. The basics behind the Snellen chart is that there are eleven lines of block letters, where the first line consists of a large letter, and subsequent rows have increasing numbers of letters that decrease in size. The distance that the eye perceives the chart is important as well, with patients being 6 meters or 20 feet away or using a mirror to mimic the distance in clinical settings that do not have the spatial capacity to distance the patients 20 feet away. Important to note is that visual acuity is indicated by the smallest row that can be read accurately and the standard reference that is considered “normal” visual acuity for healthy eyes is 20/20 or 6/6, however note that generally healthy individuals have vision that is greater than the reference VA. 6/60 or 20/200 is considered “legally blind” and this acuity represents the largest letter on the Snellen chart. However, due to the charts lack of precision and high test-retest reliability when dealing with patients with low vision, it is not used in clinical trials. The test-retest reliability is defined as the score of VA tested multiple times on the same chart with the same patient. With Snellen chart, there can be a discrepancy of up to 1 to 2 rows, from one test to the next and would not be considered vision lost or gained but rather this
discrepancy would be solely based on chance. Also, the Snellen chart follows a geometric sequence which is not linear and makes its use in calculations very difficult.

In 1976 Bailey–Lovie developed a new design that would negate the limitations of the Snellen chart, by being more precise and reducing variability (with logMAR chart the test-retest reliability is $\pm 0.07$ logMAR to $\pm 0.16$ logMAR compared to the Snellen chart of $\pm 0.29$ to $\pm 0.33$ logMAR unit). The charts that were developed with the ideas from Bailey–Lovie, are classified as “logMAR charts”, since the charts provide VA on a logarithmic scale. With logMAR charts, the measure is more precise as the ophthalmologist can measure vision letter by letter on the chart, rather than row-by-row as on the Snellen chart, with each letter having a value of 0.02 logMAR. The logMAR charts use a 5 letter per line scheme measuring the acuity letter by letter, which allows for more accurate measure of visual acuity then the Snellen method. A Snellen score of 6/6 (20/20), corresponds to a LogMAR of 0. Positive logMAR values indicate vision loss, while negative values denote normal or better visual acuity. So in other words the logMAR takes the logarithm of each value and converts the geometric scale (Snellen) to a linear scale (logMAR).

With this said, it is important to note that in earlier case series, due to the logMAR charts having increased testing time and the complexity of scoring, logMAR was not typically used for routine eye examinations, and Snellen charts were used to measure VA instead. And these case series studies conclude with either “lines lost” or “lines gained” which are not scientifically relevant. However, as mentioned above due to the precision of the logMAR scale, it is used in clinical trials and cohort studies that are planned out to measure VA, because it offers a scientific equivalent for amount of “lines lost” or “lines gained.”

Taking this into account, for our thesis, it was important to choose one scale that can be effective at allowing for comparisons and analyses to be made on VA. For such a task the Snellen scale cannot be used to assess the acuity data accurately from study to study, especially in the low-vision range, due it’s a geometric nature and lack of precision, however logMAR can since it is linear in nature. Also, it is more precise and reliable
to reach a scientific conclusion then the Snellen method.\textsuperscript{83-85} However, we must be confident that we can convert from one scale to the other. There have been studies that have indicated that one can interchangeably convert from one scale to the other, because of a high correlation between the scales\textsuperscript{85}, though one should be cautious of the conversion as one method is not as reliable as the other and this could lead to methodological heterogeneity between studies.\textsuperscript{86}

### 1.4.3 Improved/maintained VA or inflammation grade

For descriptive purposes it is also important to include data from studies reporting on percentage of patients that maintained/improved inflammation grade or VA. For the definition of maintained or improved inflammation grade, it is the percentage of patients that remained at the same inflammation grade or improved in inflammation grade (ie. having less severe uveitis) after being treated. The two categories are reported together in studies because they demonstrate a positive effect of having been given treatment.

### 1.4.4 Steroid Discontinuation Rate

One of the rationales for using immunomodulators is to spare the use of other agents, such as systemic steroids, which have a wide range of adverse effects on the body. Thus, some studies measure the effectiveness of treatment using the rate at which steroid use is discontinued in patients, or if the dosage of steroid is reduced, after immunomodulatory treatment.

### 1.4.5 Reason for Discontinuation and Discontinuation rate

Reasons for immunosuppressant discontinuation and the discontinuation rate helps illuminate the relationship between treatment efficacy and rate at which a treatment is discontinued. A treatment could be effective in treating uveitis, but the adverse events could be problematic, for example, another aspect of the patient’s health could be worse after taking CsA (ie, liver dysfunction).\textsuperscript{16}
1.4.6 Adverse Events

Adverse events are an important indicator of which treatments are effective and advantageous for treating patients with uveitis. Adverse events are usually provided for descriptive purposes.
Chapter 2

2 Literature Review

The literature review has been organized by the level of evidence. First the individual studies that have been done on immunosuppressive treatments given to uveitis patients are discussed briefly. There have also been narrative reviews and a systematic review carried out on this issue, but not necessarily specific to idiopathic uveitis patients. Nonetheless, in this literature review, the various narrative reviews and the systematic review are summarized, as well as some limitations are discussed as well. Then we discuss randomized control trials (RCTs) that are beginning to emerge and we conclude with literature pertaining to the cost of immunosuppressive treatments.

2.1 Individual Observational Studies

Most of the studies conducted on treatments for uveitis were case series. There were various definitions of success amongst the studies. Effectiveness, in most studies, is measured in terms of control of ocular inflammation, visual acuity, adverse events, and steroid sparing success.

In Table 2, 4 studies are presented to showcase the efficacy of 4 different treatments and the variety of studies encountered. While the presented studies may be valid in their own right, they do not specifically look at the patient population we are investigating, rather studies look at the entire uveitis or a subset of the population. For example, Bietti et al (1976)\textsuperscript{87} look at the uveitis patients that have Bechet disease, which is a type of uveitis with a known cause or Doycheva et al (2007)\textsuperscript{39} specifically look at the children population with uveitis. Basically, the idea presented across with Table 2 is that studies are diverse with their choice of patient population, however, there are studies that look at a specific patient populations. Thus, organizing and systematically retrieving and reviewing the literature would help paint a better picture of efficacy specific to idiopathic uveitis patients. In addition, a meta-analysis can be conducted to obtain a standardized efficacy (pooled analysis), measured in units of effectiveness that can be compared across studies and used in a cost-effectiveness analysis as well.
Table 2: Some Observational Studies and Their Findings

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Author</th>
<th>Study and Sample Size</th>
<th>Inflammation Grade change within 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Davatchi et al, 2003&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Prospective cohort Study, comparative n=23 Behçet patients associated chronic uveitis; historic series: 297 Behçet associated uveitis</td>
<td>Decrease in Inflammation Grade, used with low dosage of steroids</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Bietti et al, 1976&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Case series n=23 Behçet patients associated posterior uveitis; women 21.7%</td>
<td>--</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>BenEzra D. et al, 1988&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Randomized Control Trial (RCT) n=40 Behçet patients</td>
<td>Did RCT study comparing cyclosporine to Chlorambucil/steroid: Found cyclosporine to be more effective in 3 year follow-up, but greater side effects</td>
</tr>
<tr>
<td>Mycophenolate Mofetil</td>
<td>Doycheva et al, 2007&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Case series n=17 patients with chronic uveitis in children (32 eyes); mean age 8; women 41.2%</td>
<td>Improvement in the overall inflammation grade, but limited due to small sample size.</td>
</tr>
</tbody>
</table>

2.2 Review of Narrative Reviews on Uveitis

Studies have been conducted on the majority of idiopathic uveitis treatments. These were mainly in the form of patient records, case series, and some retrospective and prospective cohort studies. This indicates that the quality of the literature is low to moderate in regards to treating patients with idiopathic uveitis. Many narrative reviews have also been conducted in this subject area. These reviews tried to establish the use of immunosuppressive treatment using the literature, however, since subjectivity and a lack of transparency are inherent in the narrative review approach, these reviews were not systematic, and thus have significant disadvantages. Detailed explanations of the findings for each review are examined below, to present a better picture for the justification of a systematic review and meta-analysis.

The format of these reviews are generally the same; an introduction of the topic is given and a description of each treatment is provided, using studies that they deemed appropriate for each treatment group. Most of the reviews conclude that more needs to be done to understand which treatment is best for treating patients with idiopathic uveitis. Also worth noting is that some reviews generalize the disease as ocular inflammation, instead of the specific disease types, which limits their usefulness in drawing conclusions for any one particular disease, such as idiopathic uveitis.
2.2.1 A Cross-sectional Study of the Current Treatment Pattern in Non-infectious Uveitis Among Specialists in the United States

Nguyen et al (2011)\textsuperscript{88} looked at the uveitis treatment patterns of 60 ophthalmologists, comparing their behaviours to the requirements suggested by guidelines that were developed by an expert panel in 2000.\textsuperscript{16} The study looked at the actual practice patterns of physicians treating uveitis, with a particular focus on steroid usage in patients. The expert panel established that steroids were the only agents approved for the treatment of uveitis by the Food and Drug Administration, and steroids were the most frequently prescribed treatment in the study population. The panel recommended that patients be treated and maintained with less than 10 mg/day of prednisone, which would allow for lower severity of the disease and, more importantly, would lower the frequency of side effects. However, this study found that steroid doses greater than 30mg were used in about 60\% of patients for more than 1.5 years, and only 12\% of patients were treated with immunomodulators. Furthermore, 3 out of 4 physicians were not aware of the treatment guidelines for uveitis.

The study by Nguyen et al (2011)\textsuperscript{88} concluded that there is need for education about the guidelines for uveitis treatment in the medical community. Even though the guidelines (ie, narrative review) are not based on a systematic approach, but rather an expert panel, there is a need for greater awareness on the subject so more patients can access the recommended type of treatment. Guidelines based on evidence would be more helpful for policy makers and for every day practice by physicians.

2.2.2 Immunomodulatory Therapy for the Treatment of Ocular Inflammatory Disease: Evidence-based Medicine Recommendations for Use

The goal of this study was to provide comprehensive guidelines for the use of immunosuppressive treatment for specific ocular inflammatory diseases. In order to accomplish this, Kim and Foster (2006)\textsuperscript{89} summarized the current evidence in the literature.
Recommendations for the use of each treatment group depended on the strength of the recommendations (either supporting or refuting a specific therapy) and on the quality of the evidence (type of scientific evidence or trial). Table 3, which explains the recommendation classifications, was taken from the study.

**Table 3: Recommendation of Quality Levels adapted from Kim and Foster (2006)**

<table>
<thead>
<tr>
<th>Strength Classification</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong evidence of efficacy, substantial clinical benefit to support recommendation for use; should ALWAYS be offered</td>
</tr>
<tr>
<td>B</td>
<td>Moderate to strong evidence of efficacy, only limited clinical benefit to support recommendation for use; should generally be offered</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence to support recommendation for or against use or evidence of efficacy may not outweigh adverse outcomes; optional use</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence of lack of efficacy or of adverse outcome supports a recommendation against use; should generally not be offered</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence of lack of efficacy or of adverse outcome supports recommendation against use; should NEVER be offered</td>
</tr>
</tbody>
</table>

Table 4, on the following page, summarizes what Kim and Foster (2006) found in the literature for each treatment group.
Table 4: Findings from Kim and Foster (2006)\textsuperscript{89}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initial Dose</th>
<th># of studies in this review</th>
<th>Adverse events</th>
<th>Improved visual acuity</th>
<th>Decreased inflammation</th>
<th>Steroid-sparing response</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>7.5mg once per week</td>
<td>7</td>
<td>10-25% – fatigue, nausea, stomach ache, and anorexia</td>
<td>90%*</td>
<td>76%*</td>
<td>56%*</td>
<td>B2 – Is useful in treating patients that may be intolerant to steroids</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1 to 3mg/kg/d</td>
<td>7</td>
<td>Discontinuation due to gastrointestinal side effects – 15% to 30%</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>B1 – Is appropriate to use with some uveitis conditions and can be used with low-dose of steroids.</td>
</tr>
<tr>
<td>Mycophenolate Mofetil</td>
<td>1g twice daily</td>
<td>5</td>
<td>Gastrointestinal side effects – 31%</td>
<td>--</td>
<td>65%*</td>
<td>54%*</td>
<td>B2 – MMF could be used if patients have failed combination treatment</td>
</tr>
<tr>
<td>CsA</td>
<td>2 to 5mg/kg/d</td>
<td>27</td>
<td>Renal toxicity</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>B1 – Low-dose CsA can be considered first line defense with or without steroids.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1 to 3mg/kg/d</td>
<td>10</td>
<td>Infections</td>
<td>--</td>
<td>68%*</td>
<td>55%</td>
<td>C2</td>
</tr>
</tbody>
</table>

*values obtained from 1 study

Kim and Foster (2006)\textsuperscript{89} used the studies from their literature review to formulate their recommendations. The most studied treatment in their review was CsA, which 27 studies examined. From their review, it is clear that both Azathioprine and CsA are considered effective in treating patients with ocular inflammatory disease. In some cases, they also indicate the percentage of patients that experienced controlled inflammation or better visual acuity as a result of the treatment. Another key factor the review examined is the percentage of patients that were able to decrease their use of steroids as a result of the treatment.
2.2.2.1 Limitations

Though the study by Kim and Foster (2006)\textsuperscript{89} reviewed the treatments for ocular inflammatory disease in general, it did not specify which treatment group could be more helpful for specific disease types (eg, idiopathic uveitis). Furthermore, they did not include any methods or explanation for the criteria or suitability of the studies chosen in each treatment group, which could create a bias towards any number of variables. A systematic approach would help mediate these biases.

This review also had a broad range for disease type and did not specify which disease each study looked at. The results for the different disease types were combined, and conclusions were drawn for the overall effectiveness of each treatment for ocular inflammatory disease in general. This could lead to doubt in the results, and the findings could be inaccurate for patients with idiopathic uveitis. Consequently, because they combined patient characteristics, this review cannot be used to directly draw conclusions about the efficacy of the treatments for any specific disease.

2.2.3 Review of Immunosuppressive Drug Therapy in Uveitis

Dunn’s review examined the need for immunosuppressive treatment for uveitis patients, noting that the results for efficacy and safety of such treatments are often limited by the small sample size, weak study quality, absence of control participants, and changes in natural course of uveitis.\textsuperscript{90}

In this review, a literature search was conducted to examine studies published from 2001. The summary of each treatment is similar to the review by Kim and Foster (2006)\textsuperscript{89}. However, Dunn (2004)\textsuperscript{90} only used 2 to 3 studies for each treatment group to evaluate the effectiveness of each treatment. This could lead to bias, as the studies chosen could be positive in nature and the patient population may not be homogenous. Also, as with the previous review, no concrete evidence was shown regarding which treatment was better for treating patients with uveitis or which treatment was best able to reduce inflammation. This may be explained by the lack of homogeneity in the studies in respect to the treatment group, patient population, or disease characteristics. Dunn noted that it is difficult to know the treatment variables, because the studies were limited by the
difficulty in enrolling large numbers of patients in clinical uveitis trials, and the absence of a “gold standard” treatment with which to compare the other treatments. These limitations can hinder the ability to determine which treatment is best for specific disease types (eg, idiopathic uveitis). Dunn’s review stated that standardized diagnostic criteria for various types of uveitis, as exists for rheumatologic diseases, would help in the development of clinical trials for drug treatment. The study also tried to provide methodology that could help in deciding which treatment is most effective. However, since there is quite a bit of literature that is reviewable, one could simply conduct a systematic review/meta-analysis to add knowledge to this field.

### 2.2.4 Cutting-edge Issues in Autoimmune Uveitis

Levy et al (2011)\(^91\), like the others, emphasized the need to investigate the different treatments and analyze their effectiveness, as well as their side effects, to better understand how to treat patients with uveitis. The review also suggested that newer ways to determine the effectiveness of treatments are needed in order to make the best judgement about which treatments work the best for these patients. Once again, this review was very general regarding patient characteristics, and the studies they used to summarize the treatments include the entire patient population with ocular disease.\(^91\)

### 2.2.5 Use of Immunosuppressive Agents in Uveitis

Lustig and Cunningham (2003)\(^92\) examined the studies from the 5 years preceding the study's publication date. This review looked at a few studies for each different uveitis treatment (on average, 3-4 studies/treatment), and discussed similar studies to the previously mentioned reviews. As with the other reviews, this could result in bias when summarizing the findings to specific patient characteristics.\(^92\)
Table 5 below contains a summary of each treatment described by this review.

### Table 5: Findings from Lustig and Cunningham (2003)\(^\text{92}\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initial Dose</th>
<th># of studies in this review</th>
<th>Adverse events</th>
<th>Improved visual acuity</th>
<th>Decreased inflammation</th>
<th>Steroid-sparing response</th>
<th>Cost/ year US$?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>7.5 mg once per week</td>
<td>3</td>
<td>Serious side effects in 8.1% of patients</td>
<td>90%*</td>
<td>76%*</td>
<td>56%*</td>
<td>763</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1 to 3mg/kg/d</td>
<td>3</td>
<td>25%-leukopenia, abnormal LFTs, malaise and dizziness</td>
<td>--</td>
<td>--</td>
<td>47%</td>
<td>763</td>
</tr>
<tr>
<td>Mycophenolate Mofetil</td>
<td>1 g twice daily</td>
<td>5</td>
<td>Gastrointestinal side effects- 31%</td>
<td>94%</td>
<td>65%*</td>
<td>54%*</td>
<td>8748</td>
</tr>
<tr>
<td>CsA</td>
<td>2 to 3 mg/kg/d</td>
<td>4</td>
<td>Study 1: Serum creatinine, 53%</td>
<td>Study 1: 82%*</td>
<td>Study 2: 76%</td>
<td>Study 3: 50%</td>
<td>3252</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Study 3: 17%, included renal toxicity</td>
<td>After 6 months</td>
<td>Study 2: 92%</td>
<td>Study 3: 69%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Study 3: 69%</td>
<td>Study 3: 69%</td>
<td>Study 3: 69%</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.15 to 0.3 mg/kg/d</td>
<td>2</td>
<td>--</td>
<td>69%</td>
<td>69%</td>
<td>--</td>
<td>13,164</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1 to 3 mg/kg/d</td>
<td>10</td>
<td>Opportunistic infections</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>3600</td>
</tr>
</tbody>
</table>

While this review examined similar studies to those presented above, the key difference is that they also examined the costs associated with the different treatments. The costs noted in table 5 are based on approximately 1 year of therapy for an individual of an average weight of 70kg, using the lowest price from the website, www.cvs.com, or the Drug Topics Redbook 2003.\(^\text{92}\) From the table, it can be seen that methotrexate and azathioprine were the cheapest, while tacrolimus was the most expensive, with the lowest reported efficacy at 69% of patients experiencing improved visual acuity and decreased inflammation. CsA was the most effective in treating visual acuity, ranging from 82% to 92% improvement.
Overall, Lustig and Cunningham (2003) concluded that the choice of immunosuppressive agents is complex and dependent upon the cause and severity of uveitis, and the patient's prior response to immunosuppressive treatments.

2.2.6 Update on the Principles and Novel Local and Systemic Therapies for the Treatment of Non-infectious Uveitis

Although, similar to the other reviews, this review went further in trying to create gold standards and determine treatment regime for patients who present with non-infectious uveitis. Gallego-Pinazo et al (2013) summarized that patients who come in with uveitis that have relapsed should start treatment as follows:

1. Oral corticosteroids at low doses: Prednisone, 5-10 mg/day.

Prevention of cortisone side effects: Vitamin D + Calcium and Bisphosphonates. Cyclosporine A, 3-5 mg/kg/day in patients under 40 years of age. Methotrexate would be a good alternative to CsA.

2. Azathioprine or Mycophenolate, which are the third therapeutic stage if inflammatory episodes continue. Tacrolimus is an alternative to these, remembering not to combine it with Cyclosporine.

3. In the event of relapses despite prior treatments, Adalimumab is the treatment of choice, although there are other options (infliximab, tocilizumab, rituximab).

4. Finally, although it is preferable to avoid its use, is the combination of alkylating agents such as Chlorambucil or Cyclophosphamide.

The study further explained that after the use of corticosteroids, patients should be given CsA, and if that is not effective, azathioprine or mycophenolate should be prescribed. The fact that there are so many narrative reviews on the treatments for uveitis indicates that there is a need for a better understanding regarding the appropriate treatment for patients. This is underscored by the number of reviews that try to describe which treatment is the most effective. Although this type of review can be beneficial, without a definitive consensus on which treatment is best, it is hard to extrapolate anything concrete.
from the reviews. However, it is still interesting to see which treatments experts would recommend and in which order. They also indicate at which stages different treatments should be given, which is important for policy building, however, a more systematic approach is needed to extract the data from the literature and formulate quantifiable results.93

2.3 Prior “Guidelines” on Uveitis

As mentioned previously, the more chronic the uveitis, the more likely it is to be associated with poor visual prognosis.93 However, no specific guidelines for uveitis and its management have been consensually proposed. While the term guideline has been used loosely and often without any justification, epidemiologically speaking, these guidelines are narrative reviews. For the purpose of the literature review, the studies that have had influence and are referenced the most by other studies as guidelines in the ophthalmology world, are included within this section.

From the literature search, one specific proposed guideline that tried to encapsulate the data, was offered by Abad et al (2009)94 They attempted to describe and recommend the management of uveitis using the experience of ophthalmologists. Their definition of the “management of uveitis” consisted of the diagnostic procedure and types of anti-inflammatory treatments. Their treatment recommendation included the importance of identifying any underlying systemic diseases (ie, cause of uveitis). For each treatment group they examined the literature for the mechanism of action, pharmacokinetics, non-ophthalmic use, clinical experience for inflammatory eye disease, dosage and administration, and side effects and monitoring.94 However, Abad et al (2009)94 concluded that a higher level of evidence is essential in order for there to be uniformity in clinical practice.

In 2000, Jabs et al16 also provided recommendations for the use of immunosuppressive drugs in the treatment of patients with ocular inflammatory disorders. They had a 12-person panel of physicians with expertise in ophthalmologic, pediatric, and rheumatologic disease, in research, and in the use of immunosuppressive drugs in patient care.16 This study included the results not only from uveitis studies, but also from all
patients with ocular inflammatory disorders. The panel looked at all the studies from 1999 to 2000 that they could find through a literature review. Recommendations were evaluated according to the strength and quality of available evidence. Jabs et al (2000)\textsuperscript{16} concluded that the presence of corticosteroid side effects supports the rationale for using immunosuppressive drugs in the management of these patients.

Because of the potential for side effects, Jabs et al (2000)\textsuperscript{16} indicated that treatment must be tailored and regularly monitored. The careful use of immunosuppressive drugs for the treatment of ocular inflammatory disorders can benefit patients by providing either better control of the ocular inflammation or a decrease in the corticosteroid side effects. The study specifically recommended that the immunosuppressive be commenced if a dose greater than 10mg of prednisone was required for control of chronic inflammation.

### 2.3.1 Limitations

The two studies summarized above (Abad et al\textsuperscript{94} and Jabs et al\textsuperscript{16}) both presented logical arguments in their conclusions; however, a more systematic approach is needed to encapsulate the evidence. Their conclusions were not methodologically systematic, and their guidelines even state that the recommendations do not constitute treatment guidelines, but aim to improve the uniformity of clinical practice for the management of uveitis until higher levels of evidence are obtained. Thus, one cannot definitively conclude how to treat patients from the findings presented in these guidelines.

### 2.4 Previous Systematic Review on the Effectiveness of Immunosuppressants in the Treatment of Autoimmune Posterior Uveitis

In 2011, Pato et al\textsuperscript{95} used a more systematic approach to review the literature from 1961 until 2007, using Medline (from 1961) and EMBASE (from 1980). The purpose of this review was to try to fill the gap in the literature and provide recommendations for the use of immunosuppressant treatment, since no clear recommendation for the management of uveitis patients had been done.
There were a total of 4235 studies in their initial search. After applying the inclusion/exclusion criteria, which consisted of study type (which allowed any type of study), disease (which was autoimmune non-infectious uveitis), treatment, and outcome measures, they had a total of 265 articles. From the 265 articles, 90 studies pertained to immunosuppressive treatments. The majority of the studies were prospective studies and case series, with minimal RCTs. The authors summarized the findings of each study in a table, which can be found in their supplementary notes. However, they only summarized the most frequent etiology, the average dosage, and what outcome variables were frequently measured for each treatment studied. As explained below, this does not provide information as to which treatment is more effective in treating patients with the specific type of uveitis we are concerned about in our study.

Pato et al (2011)\textsuperscript{95} tried to formulate a more specific set of guidelines using the information they found, however, the conclusion of the study was that, overall, immunosuppressants are effective at treating patients with uveitis. Due to the limitations described in 2.4.1, they found no superiority for any individual treatment.

2.4.1 Limitations

When interpreting the summarized data in Pato et al (2011)\textsuperscript{95}, one must take into account the limitations of this systematic review. The first limitation is that they only searched 2 databases, which makes it possible that some articles were omitted. This would have restricted their findings if they had conducted a meta-analysis, but the main limitation of their study is that they were not able to conduct a meta-analysis. Consequently, since they did not extract data, but just noted what each study measured for their outcome variable, Pato et al (2011)\textsuperscript{95} could not draw any definitive conclusions; they could only summarize some of the findings. Furthermore, they were unable to analyze the data because there was no homogeneity in the studies. The authors mentioned that they were unable to recommend a drug of choice for each type of uveitis, because the studies included were of low quality and the outcome measures that were used to describe the results were highly heterogeneous. Visual acuity (VA) was used in most of the studies, but there was no uniformity in terms of the scale used to measure it. This could have been converted to a standard scale, but no attempt to do so was made. The inflammation grade and number
of relapses were other variables frequently used to assess effectiveness. In general, there was great diversity in terms of diseases involved and the outcome variables used.

Pato et al (2011)\textsuperscript{95} recommended that the measured outcome variable should be standardized, which would allow for an objective evaluation of the efficacy of drugs, and in turn, would provide more meaningful comparisons between drugs. However, doing something of this nature would require a major change in how ophthalmologists conduct their studies, and would require them to unify and publish their case series and chart reviews, with similar measures of outcome. Furthermore, in the case of VA, the measurements could be converted and standardized in the logMAR scale. So, it would have been possible to compare the different studies if the authors of the systematic review had decided to do the conversion. However, the same cannot be said for inflammation grade, as there is no standard conversion between the different scales.

The quality of the various studies was generally low to moderate. This does not indicate whether drugs are effective or not, it just means that the evidence presented in the different studies was inadequate due to poor study design of the original articles. Even though the authors prioritized RCTs, the number of RCTs in this field is minimal, because the number of patients with uveitis who need treatment is small, and diagnoses associated with uveitis are varied.

Other limitations of this key study include heterogeneity in the outcome variables as well as heterogeneity in the type of uveitis. Although many of the studies measure VA, there is wide variability regarding other outcome variables. The authors also indicated that there was no uniformity in relation to the procedures or scales used to measure the outcome variables. For example, to measure VA, some authors used the Snellen chart, others the logMAR scale, and others described “improvement” without a quantity. This heterogeneity in the outcome of measure limits the findings and makes it difficult to assess which treatment is best for patients. However, the study’s suggestion to alleviate this limitation is to create a more standardized method to measure outcome variables, allowing studies of different treatments to be compared.
The limitations of this study hampers what could have been a pioneer in the literature on uveitis. However, these limitations could be overcome by creating inclusion/exclusion criteria that limits the heterogeneity found in the literature. One could potentially do this by limiting the type of uveitis and creating criteria that allows a more homogenous population to be examined from study to study. As for the outcome variables, there may be ways to analyze the data that are heterogeneous in nature, for example, by converting the different scales for VA to a standardized logMAR scale.

All in all, the end result of Pato et al (2011)\textsuperscript{95} is a study that simply summarizes the literature. This systematic review was used to establish a good reference of studies within the subject area, but the heterogeneity within the patient population makes it harder to reach a conclusion. However, it is commendable that an attempt was made to systematically collect studies in the field of ocular inflammation.

### 2.5 Randomized Control Trials (RCTs)

Recently there have been RCTs that have been proposed to evaluate the effectiveness of various treatment methods for uveitis patients. These treatment methods include the immunosuppressive treatments described in this study but are not the focus of most RCTs. The RCTs are more focused on biologics, and as discussed in section 1.3, they are a new but more expensive method for treating patients. However, since they are a newer way of treating patients, there is more focus on the use of biologics and their effectiveness on uveitis patients.

Using the online service Clinicaltrials.gov\textsuperscript{96}, there have been no RCTs done specifically on idiopathic uveitis patients, however there have been studies done solely on uveitis patients. The Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group (2015)\textsuperscript{97} looked at uveitis patients being treated with immunosuppressive treatment alongside steroids, these patients were compared to a new therapy. There were a total of 255 patients, and the results indicated that this novel therapy helped improve vision more than the immunosuppressive treatments. However, it should be noted that this study looked at any immunosuppressive treatment, and as noted in the trial, the immunosuppressive treatment was given as decided by the individual ophthalmologist.
This study indicates that there is still a gap in terms of which immunosuppressive treatment one should receive. This further boosts the idea that we should have some reference or resource that one can use to help build a more appropriate RCT, with specific immunosuppressive treatment.

According to Clinicaltrials.gov, there are roughly 5 new RCTs recruiting patients for uveitis, with some specially examining the immunosuppressive treatments that we are examining in this thesis. The earliest completion date for one of the RCTs is 2018, so with the results and conclusions of this study, it could help the RCTs have a better picture of the treatments, with a more evidence-based approach to existing literature. However, it is important to note that none of the RCTs look at specifically idiopathic uveitis patients but rather on the uveitis population as a whole, this is something that sets this study apart even from the RCTs.

2.6 Previous “Economic Evaluations”

There have been no specific cost-effectiveness analyses conducted regarding treatments for uveitis. Though, as discussed earlier, there was one study that included the costs of treatment, it was not the focus of the study. There is only one other economic evaluation study that examined the costs of the treatments for uveitis, which is summarized below. Aside from these 2 studies, no other economic evaluations related to the treatments for uveitis have been done.

2.6.1 Informal Health Care — Expert Opinion

Heo et al (2012) examined the costs of treatment, however, they did not state where the cost data was taken from or how it was calculated. They estimated the annual medical spending on a uveitis patient with varying treatments. Table 6 below illustrates the data that was captured from this review:
Table 6: Cost of Treatments based on Heo et al (2012)\textsuperscript{21}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost (per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>$68</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>$92-132</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>$1948-3400</td>
</tr>
<tr>
<td>Mycophenolate Mofetil</td>
<td>$3600</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>$15,000</td>
</tr>
</tbody>
</table>

*costs depend on the frequency of use and dosage (not shown in the review)*

This study demonstrated that biologics have a significantly higher cost compared to standard therapy, which creates a barrier for the use of biologics in treating uveitis.

However, this review did not conduct a cost-effectiveness analysis. Although the authors mentioned that cost-effectiveness is low for biologics, they did not provide any measure, such as a relative/standardized effectiveness unit (QALY). They also failed to mention where they retrieved the data from, which could potentially lead to bias in the cost data.

2.6.2 Limitations

Overall, this review was not very elaborative on how one treatment is comparable to another in terms of cost-effectiveness. Though the cost data is provided, it is still very questionable as to where the data was obtained. However, the study does look at the costs of treatment per year, and it attempts to investigate which treatment should be more readily used based on cost.

2.7 Cost and Effectiveness Based on Data Collected Through Surveys

2.7.1 Survey Given to the American Uveitis Society

In this study, Esterberg et al (2012)\textsuperscript{98} conducted a survey to determine uveitis specialists’ practice patterns, preferences, and perceptions of therapies other than corticosteroids for initial use in chronic non-infectious uveitis. They distributed the survey to 205 members of the American Uveitis Society, of which 45 responded and among which 3% were Canadian uveitis specialists. The survey asked about the effectiveness of treatments using
an effectiveness rating (0 to 4), which was defined as the ability to control ocular inflammation and successfully taper corticosteroids to a maintainable dose. The survey also asked which factors limited the specialists’ use of a specific treatment; one such factor was cost.

Table 7: Main Results from Esterberg et al (2012)\textsuperscript{98}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Favourable for first line of treatment for Anterior Uveitis</th>
<th>Mean Anterior Effectiveness Rating (p&lt;0.001)*</th>
<th>Too expensive- Reason for not pre-scribing a specific immunomodulatory treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>0.6</td>
<td>3</td>
<td>Reference group, least costly</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0.07</td>
<td>2</td>
<td>0%</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0.05</td>
<td>2</td>
<td>13%</td>
</tr>
<tr>
<td>Mycophenolate Mofetil</td>
<td>0.13</td>
<td>3</td>
<td>40%</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0.06</td>
<td>4</td>
<td>56%</td>
</tr>
</tbody>
</table>

*Effectiveness Rating: Was determined in the survey by each individual Uveitis Specialist (1=not effective, 2=somewhat effective, 3= mostly effective, 4= very effective).

+Cost was another subjective measure, which was asked in the survey to distinguish reasons why a specific treatment was favoured over another.

The reason this study was included in this literature review was to look at the data provided by uveitis specialists and examine how subjective the treatment given to a patient is. In this study, the authors looked at the treatments with respect to the specific anatomy of the disease, with results for anterior uveitis shown above in Table 7. Based on this data, uveitis specialists considered methotrexate the primary treatment for uveitis among the immunomodulators (Column 2: methotrexate is considered favourable for first line of treatment among 60% of respondents), even though its effectiveness is not the best (Column 3). A large reason for this can be attributed to the cost of the treatment, as methotrexate is the least costly of the more effective treatments. This demonstrates that cost is a key factor in the choice of treatment by uveitis specialists. However, this choice is very subjective and should be examined in a more systematic way to create a concrete basis for choosing one treatment over another.

2.7.2 Limitations

This study examined the patterns of which treatments uveitis specialists would choose to treat patients with uveitis. Though the respondents indicated they would use
immunosuppressive treatments 100% of the time once the 10mg/day corticosteroids treatment was exceeded, the primary cause of concern is the study’s small sample size (only 45 respondents). This concern is further highlighted when these survey results are compared with the results from a survey conducted on the ophthalmology population in the USA, which found that steroid-sparing immunosuppressive treatments were rarely used, and an average prednisone maintenance dose of 34mg/day was reported.\(^9\) Thus, one must ask if more concrete evidence-based guidelines are necessary to maintain uniformity in uveitis care, in order to ensure that patients with similar characteristics are treated similarly from tertiary care to population based primary care.

### 2.8 Conclusion

The primary conclusion is that treatment choice is dependent on the uveitis specialist, and can vary depending on their opinion. However, with the help of a systematic review, a more concrete basis for decision-making can be used to create guidelines that all uveitis specialists can follow to make the treatment of uveitis more uniform. Furthermore, this would enable better judgement when considering the costs and effectiveness of different treatments. This leads into Chapter 3, the justifications and objectives of our study.
Chapter 3

3 Justification and Objectives

3.1 Justification for This Study

Having summarized the entirety of the relevant literature in Chapter 2, the rationale for this thesis becomes apparent. The lack of comparability within and between studies requires specific steps to allow for the accurate assessment of the effectiveness of uveitis treatments.

As mentioned above, the lack of existing RCTs in the subject area, due to sample size constraints and heterogeneity in etiology and measure of outcome, makes the case stronger for conducting a systematic review and meta-analysis. The required information can be gathered from existing literature and used to determine which treatment is best for treating patients with uveitis. However, there have been new developments in the field, and new RCTs are underway.

All treatments being studied have been shown to be effective in treating patients with severe idiopathic posterior uveitis. However, the literature mainly consists of chart reviews or case series with very limited sample sizes, and a mixed group of individuals in each study (ie, mixture of patients with different severity of disease, cause of disease, and difference in location).

Moreover, no one standard definition of success is used in the literature; effectiveness is measured in terms of visual acuity in some studies, inflammation grade in others, and corticosteroid-sparing rate in others. This leads to comparability issues, which makes it hard to compare separate studies and their various treatments. It also makes it unclear which treatment is more effective at treating patients with similar disease attributes. Creating a more specific set of inclusion/exclusion questions will make it easier to compare different studies that contain more homogenous patient populations.

The Canadian Uveitis Society (CUS) is the key stakeholder in this study. The leaders of the Canadian Uveitis Society are also members of the Canada Ophthalmology Society
(COS), and they can put guidelines in place that shift the way all ophthalmologists treat patients with this disease. The establishment of these guidelines is important for uveitis treatment in Canada, as the treatment given currently depends on the ophthalmologist. Having clear guidelines in place would result in the best possible outcome for patients with idiopathic uveitis.

3.2 Case for Why a Meta-analysis is needed

As indicated in Chapter 2, there have been many reviews on this subject area, dating back as far as 1985. There are so many review articles with exactly the same studies, and most of them come to similar conclusions, emphasizing the importance of forming evidence-based guidelines that accurately assess which treatment is ideal for treating the desired patients.

From the literature review in Chapter 2, it is clear that observational studies individually are not powerful enough, in part because they do not include a large enough sample of patients and in part because of the heterogeneity in the patient and outcome characteristics. In addition, the reviews and guidelines offered in the observational studies are not able to draw conclusions, as the literature does not have a standardized way to measure effectiveness of treatments. This gap in the literature prompted the systematic review that attempted to encompass all the available data about treatments for uveitis patients, specifically those with idiopathic posterior uveitis. However, due to the heterogeneity in the study outcomes and patient characteristics, a conclusion regarding the best treatment could not be determined. This begs the question, if a more specific group of patients with a main outcome of measure are studied, could we form a more concrete conclusion that might allow us to create guidelines and policy? This thesis was undertaken to answer this question, using a systematic review and meta-analysis. Other means to find the best treatment, such as RCTs, were not an option at this time, since it is not possible to gather the required patient sample size with similar patient characteristics and administer an array of treatments in a short amount of time.
3.3 Thesis Objectives

3.3.1 Objective 1 – Systematic Review
To systematically review the literature to summarize the effectiveness and adverse events of the different treatments used for patients with non-infectious idiopathic uveitis. For descriptive purposes, the outcomes that summarize the effectiveness of the treatment groups is outlined in section 1.4.

3.3.2 Objective 2 – Meta-analysis
a) To systematically identify, review, and quantitatively synthesize the evidence available pertaining to the pre- and post-change in VA after different immunosuppressive treatments are administered.

b) To explore and categorize other factors that may contribute to differences seen in VA after treatment is administered to patients, including location of disease, age, previous treatment given, and primary immunosuppressive treatment given.

c) To systematically identify, review, and quantitatively synthesize the evidence available pertaining to the pre- and post-change in inflammation grade after different immunosuppressive treatments are administered. This can be done if there are enough studies that have the same standardized scale for inflammation grade.

3.4 Patient Characteristics
An important component to this study is the ability to specify and focus on the patient population that is most in need of a specific immunosuppressive treatment. This patient population consists of:

1) Patients of any age.

2) Patients that have either posterior, intermediate or panuveitis (anterior uveitis responds to simple steroid treatment, since it is mainly acute uveitis, and thus studies looking solely at anterior uveitis patients will be excluded).
3) Patients that have chronic non-infectious idiopathic uveitis.

4) Patients that were given oral immunosuppressive treatment by an ophthalmologist.

The studies included will also have a percentage of patients with other disease types, or where the location of the disease could include anterior uveitis patients, however, this is only if the majority of the patients in the study were patients with intermediate or posterior non-infectious idiopathic uveitis. This will ensure that the patient population is similar, so the various studies will be more comparable to each other.

3.5 Primary Outcome of Interest for Meta-analysis

For the completion of Objective 2a and b, as outlined in section 3.3.2, efficacy of treatments will be measured by visual acuity (VA), measured in logMAR. The unit of measure for effectiveness is the difference between pre-logMAR and post-logMAR once treatment is given and the weighted mean difference of logMAR will be the effect size. This will be used to pool the data from the various studies and allow for comparability among the treatment groups, using subgroup analysis. As discussed in detail in section 1.4.2, the reason this measure is used is because the different scales used in other studies can be easily converted to logMAR, so comparability exists and logMAR scale gives a more precise and accurate assessment of change in vision. For a more detailed discussion of logMAR and VA, see section 1.4.2.

Secondary Outcome: Inflammation grade will also be pooled from the various studies if there is enough data available. This secondary outcome will provide a means to measure the change in pre- and post-inflammation grade (based on a 0 to 4 scale), indicating whether an increase or decrease in inflammation occurred after treatment. The inflammation grade measures severity of disease. The measure of inflammation ranges from 0 to 4+. Patients with a grade 3 or more are considered to have severe uveitis. If the treatment shows a mean change in inflammation of 2 grades or more, then the treatment is deemed effective. See section 1.4.1 for more detail.
Chapter 4

4 Literature Review for Methodology

4.1 Overview of Meta-analysis

Before we go into the methodology, it is important to understand how to conduct a meta-analysis and know some of the terminology that is used within a meta-analysis. Thus, this chapter will do a brief introduction of the methodology used in this thesis and how to interpret a meta-analysis.

A meta-analysis can be conducted on an area of research where the studies have low power due to small sample size or intervention effect. When the studies are combined, the estimated intervention effect becomes more precise, and power is increased if the studies have similar variability and similar effects. However, when the results of the combined studies show inconsistency/heterogeneity, represented as $I^2$, then measures must be taken to assess where the heterogeneity originates. There are 2 methods that can be used to assess heterogeneity; the first is a subgroup analysis, and the second is meta-regression. Subgroup analysis allows you to measure the variability using subgroups that may be present in the collected data, which could account for the heterogeneity. Meta-regression uses regression to evaluate if a relationship exists between 1 or more covariates (moderators) and the effect size in the studies.

4.2 Mechanics of Meta-analysis

Once the summary data is collected, an understanding of the mechanics of meta-analysis will allow one to assess the data smoothly and accurately. The first step is to understand how the summary data can be used to obtain an effect size for each study.

4.2.1 What is Effect Size?

Effect size is what encodes the relationship of interest into a common index.99
It is important to determine an index of how the effect size will be measured. The effect size can be presented in many ways; it depends on the data that is extracted. Some effect size indexes include standardized mean difference (SMD), correlation coefficient, and effect size based on binary data (ie, risk ratio or odds ratio). Choosing the index is straightforward, as the summary data in general will dictate the index. For example, if the data are based on a standardized meaningful outcome, then using a raw mean difference (WMD) could be beneficial as the outcome is standardized and is on a meaningful scale that is widely used, like blood pressure. However, in the case of other indexes like binary, where there are many choices like odds ratio, relative risk, risk differences, or number needed to treat, it becomes rather controversial to choose an index and care must be taken in order to pick the index for the meta-analysis.

4.2.2 Precision

Variance, standard error, and confidence intervals are all measures of precision. How precise the effect size of a study is depends on a variety of things, however, the rule of thumb is the greater the sample size, the narrower the confidence intervals and the more precise the effect size is. As the sample size is reduced, it loses power and the confidence intervals become larger, and therefore the overall precision is lower. This relationship is important for identifying error within studies, which is needed to calculate the summary effect size and confidence intervals found in a forest plot. In addition, study design could affect the precision as well. For example, a cluster trial would have larger variance than a study with 2 independent groups, since an entire cluster of participants is assigned to one condition or another. It is important to understand that both sample size and study design can affect precision, which is intrinsic to that study.

The forest plot consists of the reviewed studies and their effect sizes, their precision, which is indicated by confidence intervals, the inverse of the study’s variance by the area of the box, and the inverse of the study’s error indicated by any side of the box.

Another key component of a meta-analysis is the variance or error that is within each study. In this study, the variance of the difference was calculated in STATA by using the individual standard deviations for the pre-post logMAR.
4.2.3 True Effect Size and Summary Effect Size

True effect size is the effect size in the underlying population for that study, and it is the effect size that we would observe if the study had an infinitely large sample size (thus, no error within or between studies if assuming random effects model). A study’s observed effect size is the effect size that is actually observed. The summary effect size is the calculated weighted mean of the observed effect sizes of all the studies combined. The true overall effect size is the summary effect if all the studies had a common effect size (ie, true effect size). These calculations were done using Stata.\textsuperscript{102} Below, we explain the different models available to compute the summary effect size, the precision associated with each model, and which model was chosen for our study.

4.2.4 How to Measure a Summary Effect Size (Fixed vs. Random Effects Model)

When computing the summary effect size and assessing heterogeneity, it is important to note that the same methodology is used no matter which index is chosen.\textsuperscript{103} For the meta-analysis, there are 2 models for computing the summary effect size. One is the fixed effects model and the other is the random effects model.\textsuperscript{103} Fixed effect assumes that the true effect size is the same with every study and the only variance that is present is due to within-study variance.\textsuperscript{103} For example, if all the studies were conducted the same way, and all the factors that could influence the effect size were the same in all the studies, then the true effect size would be the same in all studies. Under the fixed effects model, all the studies share the same true effect sizes, so the observed effect size varies from one study to the other only because of the random error intrinsic in each study. The difference seen between the observed effect size and the true effect size ($X_i$), is contributed by the error ($E_i$), thus the observed effect size ($Y_i$), is simply:

$$Y_i = X_i + E_i$$

We assume that the error is placed in a normal curve about the true effect size for each study, with the width based on the variance in that study. Performing a meta-analysis when calculating the summary effect size using the fixed effects model, we take into account the variance by taking the inverse variance, which is the weight of that study, and
multiplying it by the observed effect size. In our study, we assigned weights so we could minimize the within-study error; in other words, we tried to obtain a more precise estimate of the population effect. The next step is to take the sum of the product and divide it by the sum of the weights. Then, to determine the variance of the summary effect, we take the reciprocal of the sum of the weights. The null hypothesis that the z-test is trying to test is that the common effect is zero for the differences, or 1 for ratios.

Though the basis for the summary effect size calculation in a fixed effects model accounts for within-study error, it is not a valid reason to assume that all the studies will have the same true effect size. Unless certain, there is another model, which allows the true effect size to vary from study to study. The random effects model assumes that there may be between-study variations as well as within-study variation. This model is usually more valid, because studies may differ in study design, type of intervention, age, or another factor, and effect sizes are assumed to be different among the different studies. For example, the effect size might be higher (or lower) when the participants are older, more educated, healthier, or when a more intensive variant of an intervention is used, and so on. Because the studies will differ in the combination of participants and types of treatment, there may be different effect sizes for the different studies. A key assumption of the random effects model is that the true effect is normally distributed. For our study, we calculated the between-study variance and included that in our weight before doing any further calculations. Dersimonian and Laird (1996) have presented a method to calculate between-study variance, or the heterogeneity. This will be discussed in the next part of the thesis.

However, the main equation for the random effects model and the change from fixed effects model is the addition of the between-study variance, as shown below:

\[ Yi = X + E + B \]

So, the observed effect \( Yi \) is the true mean (X), the deviation of the study’s true mean (E), and the deviation of the study’s observed effect from the studies’ true effect (B). Weight assigned to each study via the random effects model is:
\[ W_i^* = \frac{1}{V_{yi}^*} \]

Where, \( V_{yi}^* \) is the within-study variance for study \( i \) (\( V_{yi} \)), plus the between-studies variance (\( T^2 \)),

\[ V_{yi}^* = V_{yi} + T^2 \]

And the weight is reciprocal of the \( V_{yi}^* \).

The weighted mean is calculated the same way as in the fixed effects model, taking the sum of the weight (\( W_i^* \)) and the effect size (\( Y_i \)), and then dividing that by the sum of the weights. The variance of the summary effect is estimated as the reciprocal of the sum of the weights.

Thus, the goal was to use the weight of the studies to minimize both sources of study variance. The random effects model suggests that the studies in the analysis represent a random sample of effect sizes from all the effect sizes that could have been observed.

Not only does the random effects model take the weight of the study into consideration, but it also considers the weight of the variance between one study and the other studies in the meta-analysis. In contrast, the fixed effects model uses the weight of the studies by considering sample size and only the within-study variance. If the variances between studies is large and the fixed effects model is used, then a study with a larger sample size will be assumed to possess greater precision. In reality, it means that 1 study might dictate the summary effect size. With the random effects model, that larger study will not be given as much weight depending on the between-study variance compared to the other hypothetical studies. Thus, it is more accurate to use the random effects model in the case of notable or a priori predictions of the heterogeneity of studies.

In the fixed effects model, more weight is given to studies that are more precise, because it is assumed that the true effect size is the same among all the studies. However, in the random effects model, we are looking for the mean of the distribution of the effect sizes. Since each study provides information about a different effect size, we want to make sure every effect size is taken into consideration when determining the summary effect size.
Consequently, small studies are given more weight and large studies are not given as much weight, which allows for more balance. Extreme studies lose influence when we move from the fixed to the random effects model. Confidence intervals will be larger, as there are 2 errors associated with the model, unless the between-study variance ($T^2$) is zero, then the fixed and random effects model will be the same.

Conceptually, it is important to note that if the sample size reaches infinity, it would make the error in the fixed effects model narrower. However, in the random effects model, there would need to be an infinite amount of studies for the error to narrow. The null hypothesis in the fixed effects model is that there is zero effect in every study, whereas in the random effects model, the mean effect is zero.

4.2.5 Heterogeneity

In order to understand the implications of our study, it is important to observe if there is consistency in the studies or if there is heterogeneity in the true effect sizes. This is not to be mistaken with precision since that term is solely used for within-study variance, whereas heterogeneity is used for the variation found in true effect sizes. If there is heterogeneity, can we pinpoint what is causing it? In a random effects model, we allow that the true effect size may vary from study to study, and suggest that there will be heterogeneity; therefore, heterogeneity can be defined as between-study error. However, how do we identify it in a meta-analysis?

4.2.5.1 What is heterogeneity

In the context of a meta-analysis heterogeneity is defined as statistical heterogeneity or inter-study variance. In a meta-analysis it is assumed that statistical heterogeneity is a consequence of clinical or methodological variation. Clinical variation is heterogeneity due to differentiations in interventions or patient characteristics. These variations can affect the between study variance and true treatment effect will be different study to study. This can be reduced by having stringent inclusion/exclusion criteria, which would allow for similar patient characteristics from study to study. There would still be clinical variation with the type of treatment given, since there are many in our study.
Methodological factors, such as how the outcomes are measured and defined could lead to differences in the observed treatment effects. For example, having different scales to measure VA could lead to methodological heterogeneity as one study could measure using Snellen and another via logMAR. Thus being aware of the kind of heterogeneity that could be present is important, and would allow one to choose the appropriate model to conduct their meta-analyses. If we know that there will be heterogeneity, then a random effects model would be chosen and would allow for between-study error. However, we need to know how to identify it and measure it statistically.

4.2.5.2 How to identity and measure heterogeneity

There are many methods to identify heterogeneity. One is to look at the forest plot and examine how the studies are dispersed from one another, but in order to objectively identify heterogeneity, we must separate the true variance (between-study variance) from the random error (within-study variance). For the purposes of this thesis, it not important to understand how the calculations are done, but to understand conceptually how heterogeneity is identified.

One method to identify heterogeneity is the Q method, which is the dispersion that is excess to the within-study error and is standardized, which means it is not affected by the metric of the effect index, but it suffers from low power if there are too few studies. The null hypothesis using the Q can be rejected when the p value is set at less than the alpha, which is set to 0.05. Q will follow a chi-squared distribution with degrees of freedom equal to k-1. This is called the homogeneity test; if we reject the null hypothesis, then the distribution of the effects is heterogeneous.

However, the Q statistic could be used to compute a ratio or dispersion on the same scale as the effect index itself. One such way Q is calculated is the method of moments or the DerSimonian and Laird method, which converts the Q to the same scale as the effect index. This method calculates the between-study variance found in the random effects model and the standard deviation of the summary effect size. This between-study variance is represented by $T^2$. The $T^2$ is used in the random effects model and is defined
as the between-study variance that is not explained by excess error found in the study. It is used to describe the heterogeneity found in the studies in most meta-analyses because it is easy to calculate, however, it is not the best way to discuss the variance, since it is on the same scale as the effect index and cannot make comparisons to other indexes. A new method is used to describe the heterogeneity using ratios with Q value; this value is represented as $I^2$. It allows one to make a conclusion about whether any of the total variation that we see is due to the true variation or heterogeneity. This is a way to identify heterogeneity, and the reason it is often used to talk about heterogeneity is because it is not sensitive to the number of studies, unlike the method of moments, and it is not sensitive to the metric of the effect size.

Once the heterogeneity is identified, we can further explore where the heterogeneity could be coming from. For this, there are 2 methods: subgroup analysis and meta-regression.

### 4.2.6 Subgroup Analysis

Subgroup analysis is the set of studies divided via a particular subgroup, such as treatment classes. Subgroups can be used to determine whether the heterogeneity can be explained by a particular subgroup. However, there is a lot of debate concerning the test of heterogeneity with any method in a subgroup, as subgroups may be too small to be significant or it may be unreasonable to make a comparison from one group to another (for example, 1 subgroup could contain only 2 studies, while another subgroup contains more then 10). The use of fixed effects models with subgroups has been debated for some time. However, the use of random effects models with subgroups has recently been applied, with certain assumptions. For example, if we assume that each study within the subgroup shares a common effect size, then we can apply a fixed effects model, but if we do not make that assumption, then the random effects model can be applied. With the random effects model, if we assume that the between-study variance is the same for all subgroups, then we compute the $T^2$ for the subgroups, pool them together and use the same estimate for all subgroups. If not, then we use a separate $T^2$ for each subgroup.
For the purposes of our thesis, if any between-study variance existed, for practical reasons (which will be explained below), it was assumed that it was the same. Some heterogeneity authorities do not believe that subgroup analysis is a strong measure for comparing the different subgroups due to the low number of studies per subgroup.\textsuperscript{100,101} One rule of thumb is that if there are fewer than 5 studies per subgroup, there is an assumption that the between-study variance is the same for all subgroups.\textsuperscript{101} Thus, the fixed effects method is used for subgroups; this is one of the only valid methods to test for heterogeneity, as using random effects would make the test of power even lower.\textsuperscript{101} When there are a low number of studies within a subgroup, it may be wise to just conduct a pooled meta-analysis. However, it reasonable to use the random effects model if each subgroup has more than 5 studies.\textsuperscript{100,104}

### 4.2.7 Conducting a Univariate Meta-regression with Multiple Covariates

Meta-regression in a meta-analysis assesses the relationship between study-level covariates and effect size. Meta-regression is similar to regression conducted in primary studies, the key difference being that each study is weighted, depending on which model is selected (fixed vs. random effects). Knowing which model to pick is important, as it will affect the results (more even weights among studies when using the random effects model, and larger studies do not impact the summary effect size or the regression line).

Under the null hypothesis, using the random effects model, the mean is the same for all values of the covariates.\textsuperscript{105} When conducting a random effects model meta-regression, it is important to understand some technical issues, the first being that Z-distribution is only appropriate for the fixed effects model, where the source of error is within-study.\textsuperscript{7} For the random effects model, the dispersion across the studies should be accounted for using the t-distribution. There are many methods to accomplish this, the most well-known and accepted is from Knapp and Hartung (2003).\textsuperscript{107} Two modifications are made to the standard error for the random effects model. The first is the between-study variance component, which is multiplied by a factor so it corresponds to the t-distribution rather than the Z-distribution. The second is that the test statistic is compared against the t-distribution, which expands the width of the confidence intervals and moves the p-value
away from zero. Another method, by Higgins and Thompson (2004)\textsuperscript{108}, is to bypass the sampling distribution and use a permutation test to yield a p-value. Using this test, a z-score that corresponds to the observed covariate is computed, then the covariate is randomly distributed among the studies to see what proportion yield a z-score that exceeds the one that was obtained.\textsuperscript{107} This is the true p-value.

### 4.2.8 Final Remarks for Meta-regression or Subgroup Analysis

The absence of statistical significance should never be interpreted as evidence that an effect is absent. This is important to keep in mind since power to detect heterogeneity in effect sizes or between covariates or subgroups is very low. In other words, failure to obtain a statistically significant difference among subgroups or covariates should never be interpreted as evidence that the effect is the same across subgroups or that there is no relationship between the covariate and the effect size. Also, the reverse is true, even with a statistically significant relationship between effect size and subgroups or between effect size and covariates is observational and cannot be used to prove causality. This holds true even if all studies in the analysis are RCTs. Some studies employ a strategy of starting with the fixed effects model and then modifying to use the random effects model if the test for heterogeneity is insignificant for meta-regression or subgroup analysis. This approach has significant disadvantages; instead, the model that is initially chosen should be based on knowledge of the subject matter.

### 4.2.9 Power vs. Precision

To ensure that a study has good statistical power (a sufficiently high likelihood of yielding a statistically significant result), observe whether a meta-analysis has sufficient statistical power to test the null hypothesis of no effect.\textsuperscript{99} Although it is not always mandatory to conduct a power analysis for a meta-analysis, especially one with multiple treatment groups, it can help determine whether a study is likely to yield statistically significant results. This is particularly important in primary studies. In meta-analysis, it is more appropriate to look at the effect size and its precision, as that provides a clearer indictor regarding whether or not the result was significant.
4.2.10 Publication Bias

Publication bias can have a pronounced effect on the results of a study, as some studies could have been overlooked in the screening phase, which could lead to bias that is known as publication bias. The consequences of publication bias include precision and validity. There could also be bias due to larger studies being included and smaller studies not being included because they are not as easy to find. One way to mitigate the precision issues related to publication bias is to use a random effects model to ensure that all studies are evenly weighted, but this doesn’t take into account the amount of publication bias that might exist or how the data would look if those theoretical studies were not missing.

There are methods that have been established to determine if publication bias has taken place, and some methods can even adjust for the bias. A funnel plot is used by these methods to detect any asymmetry, and to examine whether the asymmetry is due to chance. There are also tests, such as Begg and Mazumdar (1994) and Egger et al (1997). However, these methods do not provide estimates about the number or characteristics of the missing studies, nor do they provide an estimate of the underlying (biased) effect. One such method, developed by Duval and Tweedie (2000), does address these issues.
Chapter 5

5 Methods

We conducted this review in accordance with the Meta-analysis of Observational Studies (MOOSE) recommendations and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (completed checklists in Appendices A and B).

5.1 Literature Search

A comprehensive and pre-planned search strategy from 6 databases (MEDLINE, EMBASE, Cochrane Library, CINAHL, Scopus, BIOSIS and Web of Science) was created to obtain the maximum return of relevant studies related to our question. Free text key words and medical subject headings were tailored to each of the electronic databases. The search strategy was performed in collaboration with a medical librarian with searching expertise, ophthalmologists within the Canadian Uveitis Society, and information specialists. The search strategy consisted of the terms listed in Table 8 below.
Using these terms enabled the development of a comprehensive search strategy for each database, which can be found in the Appendix C. The original search was performed in June 2012, and it continued to gather articles via monthly updates until March 2013. Searches were not restricted by publication type, date or language. To ensure all relevant studies were identified, unpublished studies were also searched through manual searches of electronic abstracts and dissertations from the American Academy of Ophthalmology and the Association for Research in Vision and Ophthalmology meetings. To further ensure all studies relevant to the systematic review were included, bibliographies of eligible studies and relevant systematic reviews retrieved in the literature search were manually screened.
5.2 Eligibility Criteria

With the help of ophthalmologists within the Canadian Uveitis Society, the study eligibility criteria were established by identifying key components that needed to be fulfilled to answer our study’s question: how immunosuppressive treatments affect patients with non-infectious idiopathic uveitis. The key components consisted of patients, Intervention, Comparison, Outcomes and study design (or PICOS). These terms needed to be fleshed out completely before we could answer question. PICOS is a helpful tool to help focus on what is important to our question and create the appropriate eligibility criteria. Our eligibility criteria was:

Participants: As discussed in section 3.4, we looked at studies that specifically examined non-infectious idiopathic uveitis patients. This would ensure that the patients who were studied were the patient population that we wanted to look at, and would allow for homogeneity within the study population. Patients with uveitis that was not exclusively idiopathic in nature were included. Studies with fewer than 50% of patients with diseases other than non-infectious idiopathic uveitis were included in order to capture existing evidence from mixed populations (see Appendix D for the list of diseases that were excluded).

The focus was on posterior and intermediate uveitis patients, as they were the 2 locations of uveitis where it was most unclear regarding treatment efficacy. Studies solely focused on anterior uveitis patients were excluded because they are easier to treat, and there is little equipoise regarding treatment choices. If posterior or intermediate uveitis patients accounted for 50% or more of the patients examined within a study, then that study was included.

Interventions: The studies that examined any 1 of the 3 main groups of immunosuppressive treatment (ie, antimetabolites, alkylating agents, inhibitors of t-lymphocytes) were included. The treatment must have been orally administered (which is the most common method of administering immunosuppressive treatment) to ensure homogeneity, because some patients can be receive treatment via other means, such as injections.
**Outcomes:** Measured via changes in visual acuity (VA) and/or inflammation grade, relapse rate, corticosteroid-sparing rate, and adverse events. As discussed in section 1.4, these outcomes were specific to determining the effectiveness of the treatment given to patients and what was used in different studies to describe effectiveness. And as discussed in section 3.5, the primary main outcome of measure used for the meta-analysis was change in VA, measured in logMAR. The rest of these outcomes were used for descriptive purposes under the systematic review.

**Study Design:** All study designs were included, except narrative reviews. There were no restraints on year of publication, as any treatment given in the past or present would be administered in a similar fashion. Also, we only looked at studies from the English language. Also, studies that were done in either North America, Western Europe, Hong Kong, Japan, New Zealand, Australia or Singapore, were included. This was done as developing countries may not have similar clinical practices as these countries, and would further the clinical heterogeneity.

Therefore, this study included primary studies that assessed the effectiveness (measured via changes in visual acuity (VA) and/or inflammation grade, relapse rate, corticosteroid sparing rate, and adverse events) of treatments (antimetabolites, alkylating agents, t-lymphocyte inhibitors) for patients with non-infectious idiopathic uveitis.

### 5.3 Article Screening

Two levels of screening were performed to eliminate articles that did not meet the inclusion criteria. Level 1 consisted of screening through the titles and abstracts to seek out articles potentially relevant to the study. From the articles included in level 1, the full-text of the articles were retrieved to more closely assess inclusion and exclusion criteria for level 2 screening. Two reviewers screened citations (AC and HS) and full-text articles (SS and HS) in an independent fashion, and to examine inter-rater agreement using Cohen’s kappa coefficients. The kappa values were interpreted as follows: 0.40 to 0.59 reflected fair agreement, 0.60 to 0.74 reflected good agreement, and ≥0.75 reflected excellent agreement.¹¹²,¹¹³ Once the screening was conducted, the 2 reviewers reconciled the discrepancies through discussion. Both levels of screening were done in duplicate to
increase accuracy and reduce measurement bias. An experienced ophthalmologist (WH) was consulted to resolve any remaining disagreements.

Studies were excluded if: (i) greater than 50% of the patients were diagnosed with any of the diseases listed under Appendix D, (ii) location of disease was mainly anterior uveitis (greater than 50% of patients), (iii) studies having less than 5 patients with idiopathic uveitis, (iv) studies were conducted in developing countries, (v) the treatment was not given orally, (vi) not a primary study, and (vii) studies did not provide the outcome of interest. The entire list of inclusion/exclusion criteria for both level 1 and level 2 can be found in Appendix D.

5.4 Data Extraction for Descriptive Statistics

To extract data from the eligible studies, we created a data extraction form. Two reviewers (HS and AC) dependently conducted a “trial pilot” of the extraction form on a subset of the eligible studies. Based on the changes in the pilot study, the final version of the data extraction form was developed (see Appendix E). For the purpose of this thesis, the data extracted from the studies was organized by the treatment given to the majority of patients in a particular study. The following information was collected in the final data extraction form:

Study Characteristics: included the study design, setting/data source, and the accrual period of the study and sample size. This was relevant because it gave an idea of the types of studies we examined.

Participant Characteristics: As mentioned in section 3.4, the patient characteristics included the number of patients with idiopathic uveitis (sample size), mean age, standard deviation of age and/or the maximum and minimum age range, frequency of female patients, mean follow-up time in months, mean follow-up standard deviation and/or maximum and minimum range for follow-up time, primary cause of uveitis, with majority having idiopathic uveitis, frequency of patients with the primary cause, primary location of diseases (could be posterior uveitis, intermediate, panuveitis, or a combination
of them), frequency of patients with primary location of disease, and lastly, which if any previous treatments were given to patients before the immunosuppressive treatment.

It was important to collect these characteristics for the purposes of describing the findings in our study. They allowed us to understand the patient characteristics, and allow for comparisons to be made between patients from different treatment groups. So, where possible only data from idiopathic patients were extracted from the studies, if the results were of the entire patient population, then we made sure that 50% or greater of the patients were idiopathic in nature, which was a part of our article screening process.

*Baseline Characteristics (Before Treatment)*: included location, cause and type of uveitis, and any previous treatment given. This allowed us to ensure homogeneity was present within patient populations, as most of the data collected should have been similar.

*Treatment*: included treatment given, dosage, and length of treatment time. These variables were important to obtain, so a study with a particular treatment could be compared to another with the same treatment, knowing that the dosages were similar.

*Outcomes (after treatment)*: As discussed in section 1.4, outcomes measuring effectiveness included reduction in severity of disease indicated by frequency of patients that improved or maintained Visual Acuity and/or inflammation grade, reason for discontinuation, steroid usage, clinically-relevant adverse events and the frequency of patients that experienced each adverse event, and anything else the study used to measure outcome. For the purposes of the systematic review, all outcomes that were present in the study were extracted for descriptive purposes.

Relapse rate, corticosteroid-sparing rate, and adverse events were extracted for descriptive analysis as opposed to meta-analysis. However, relapse rate and corticosteroid-sparing rate were not included in the final descriptive statistics due to a lack of sufficient data.
5.5 Data Extraction for Meta-analysis

For this study, the primary outcome for the meta-analysis, as outlined in section 3.5, is presented in the form of pre-/post-logMAR with the respective standard deviations. This allowed us to use the unstandardized mean difference or raw mean difference because the summary data was in a meaningful scale. An SMD index was not used because we knew that some studies used different scales, which we accounted for and standardized. However, most of the data used the logMAR scale, and the studies that did not were converted to logMAR. Thus, raw mean difference was used. The unit of analysis is the pre-/post-logMAR. The advantage to this design is that each pair serves as its own control, reducing the error term and increasing the statistical power. Also, regardless of study design, the computed effect size and variance from each study could be included in the same analysis, since the scale is the same. The conversion of scales to logMAR was done in MS Excel, before being imported into Stata.

On the extraction form found in Appendix D, pre-VA and post-VA, or change in VA, were extracted as well. Alongside the VA itself, the respective standard deviations were also extracted. The majority of the data collected were taken for descriptive purposes, and pre- and post-VA became useful for the meta-analysis. As described in section 1.4.2, VA can be measured in different scales and due to the high correlation between the scales VA can be interchanged. Thus, using Table 9, VA which was not in logMAR was converted to logMAR scale and also as a rule of thumb the formula to convert from decimal to logMAR is $-\log_{10}(\text{Decimal})$.\(^{80}\)
Table 9: Visual Acuity Conversion Chart

<table>
<thead>
<tr>
<th>20 ft.</th>
<th>6 m</th>
<th>Decimal</th>
<th>4 m</th>
<th>Log MAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 / 630</td>
<td>6 / 190</td>
<td>0.032</td>
<td>4 / 125</td>
<td>+1.5</td>
</tr>
<tr>
<td>20 / 500</td>
<td>6 / 150</td>
<td>0.04</td>
<td>4 / 100</td>
<td>+1.4</td>
</tr>
<tr>
<td>20 / 400</td>
<td>6 / 120</td>
<td>0.05</td>
<td>4 / 80</td>
<td>+1.3</td>
</tr>
<tr>
<td>20 / 320</td>
<td>6 / 95</td>
<td>0.06</td>
<td>4 / 63</td>
<td>+1.2</td>
</tr>
<tr>
<td>20 / 250</td>
<td>6 / 75</td>
<td>0.08</td>
<td>4 / 50</td>
<td>+1.1</td>
</tr>
<tr>
<td>20 / 200</td>
<td>6 / 60</td>
<td>0.1</td>
<td>4 / 40</td>
<td>+1.0</td>
</tr>
<tr>
<td>20 / 160</td>
<td>6 / 48</td>
<td>0.125</td>
<td>4 / 32</td>
<td>+0.9</td>
</tr>
<tr>
<td>20 / 125</td>
<td>6 / 38</td>
<td>0.16</td>
<td>4 / 25</td>
<td>+0.8</td>
</tr>
<tr>
<td>20 / 100</td>
<td>6 / 30</td>
<td>0.2</td>
<td>4 / 20</td>
<td>+0.7</td>
</tr>
<tr>
<td>20 / 80</td>
<td>6 / 24</td>
<td>0.25</td>
<td>4 / 16</td>
<td>+0.6</td>
</tr>
<tr>
<td>20 / 63</td>
<td>6 / 19</td>
<td>0.32</td>
<td>4 / 12.5</td>
<td>+0.5</td>
</tr>
<tr>
<td>20 / 50</td>
<td>6 / 15</td>
<td>0.4</td>
<td>4 / 10</td>
<td>+0.4</td>
</tr>
<tr>
<td>20 / 40</td>
<td>6 / 12</td>
<td>0.5</td>
<td>4 / 8</td>
<td>+0.3</td>
</tr>
<tr>
<td>20 / 32</td>
<td>6 / 9.5</td>
<td>0.63</td>
<td>4 / 6.3</td>
<td>+0.2</td>
</tr>
<tr>
<td>20 / 25</td>
<td>6 / 7.5</td>
<td>0.8</td>
<td>4 / 5</td>
<td>+0.1</td>
</tr>
<tr>
<td>20 / 20</td>
<td>6 / 6</td>
<td>1.0</td>
<td>4 / 4</td>
<td>0</td>
</tr>
<tr>
<td>20 / 16</td>
<td>6 / 4.8</td>
<td>1.25</td>
<td>4 / 3.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>20 / 12.5</td>
<td>6 / 3.8</td>
<td>1.6</td>
<td>4 / 2.5</td>
<td>-0.2</td>
</tr>
<tr>
<td>20 / 10</td>
<td>6 / 3</td>
<td>2.0</td>
<td>4 / 2</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

As discussed in section 1.4.2., in order for analysis to be conducted on VA, logMAR is the most reliable and precise scale because of its logarithmic nature, which offers a more accurate estimate of VA compared to other scales used to measure VA. On the logMAR scale, better vision means a lower logMAR value (ie, a -0.01 change in logMAR means an improvement in visual acuity).

In studies that did not record the measure of visual acuity outcome directly, it was extrapolated from the graphs within the studies. This was done using online software called graph digitizer™, which allowed us to input the data from the x-axis and the y-axis to re-create the graphs to scale. Then, by manually clicking on the graph at the point of importance, the software produced the pre- and the post-value of VA for the missing data. In addition, for data reported as means, standard deviation was also recorded. If standard deviation was not reported for outcome measures, raw data was extracted from graphs.
and used to calculate standard deviation where available. The standard deviation of age was also found for studies that did not report it, using range, which is another measure of variability. In some cases, we also attempted to gather missing information by contacting the study authors.

5.6 Quality Assessment

We used the Downs and Black scale to evaluate the risk of bias in the included studies. Deek et al (2003)\textsuperscript{115} conducted a systematic review where they identified 182 quality assessment tools for assessing non-randomized studies. From 182, 14 tools were considered the “best tools” according to their pre-specified criteria, but only 5 were considered suitable for systemic reviews. From the 5, 2 tools, the Newcastle-Ottawa scale and the Downs and Black scale, were found to be able to differentiate between the reporting bias, selection bias and external bias. From these, Downs and Black scale provides a numeric score for overall study quality that is easy to interpret.

We used the Downs and Black scale to access methodological quality and evaluate the risk of bias in the studies we included, because it has excellent test-retest reliability ($r = 0.88$), inter-rater reliability ($r = 0.75$) and internal consistency (Kuder-Richardson 20 $r = 0.89$).\textsuperscript{116} The Downs and Black scale can be used to assess both randomized and non-randomized studies. It contains 27 questions, divided among the following 5 subsections:

a. Reporting (10 questions): Is the information provided in the study sufficient for the reader to make an unbiased assessment of the findings?

b. External Validity (3 questions): Examines the extent to which the findings of the study subjects can be generalized to the population.

c. Internal Validity/Bias (7 questions): Examines whether the measurement of the intervention and outcome of the study are biased.

d. Internal Validity/Confounding (6 questions): Examines whether selection bias is present within the study.
e. Power (1 question): Assesses whether the negative findings in the study are due to chance.

Total scores usually range from 0 to 31; however, we adapted the final question relating to power from a scoring scale of 0 to 5 to a scale of 0 to 1. Other studies have modified the Downs and Black, however, it should be noted that when changing or modifying the tool, it compromises the reliability and validity. Thus our modifications could have comprised the reliability and validity. The modified Downs and Black scale (maximum score of 28) in other studies is evaluated with grade of “excellent” if studies scored 24–28 points, “good” for 19–23 points, “fair” for 14–18 points or “poor” if <14 points. For our study we took the frequency that was translated from the grades provided by Tully et al (2015) to give meaning to our results, and differentiate the quality of our studies.

A study scored 1 if a power or sample size calculation was conducted, while 0 was assigned if no calculation was done. Therefore, our adapted Downs and Black scale for RCT ranged from 0 to 27, with a higher score indicating higher study quality. The quality of an RCT would be “excellent” if the a frequency of 83% to 100% was obtained, “good” would be 65% to 82%, “fair” if frequency would be 51% to 64% points or “poor” if <50%.

For observational studies, 3 questions from the internal validity section were removed, along with 2 questions from the selection bias section, as they were topic sensitive and pertained mainly to randomized trials. Questions 14-16 were removed from internal validity, because they pertained to whether the patients and those measuring the main outcome were blinded by the intervention given. In the majority of the studies we examined, patients were given treatment due to the severity of the disease and both the administrator and the patient knew which treatment they received. Questions 23 and 24 were removed from selection bias, because they referred to patients being randomized, which did not take place in the majority of the observational studies. Therefore, our adapted Downs and Black scale for observational studies ranged from 0 to 22. The quality of an observational would be “excellent” if the a frequency of 83% to 100% was
obtained, “good” would be 65% to 82%, “moderate” if frequency would be 51% to 64% points or “poor” if <50%.

For the purpose of this thesis, when organizing the figures, the 4 categories were displayed with the frequency of studies that had been assigned “yes” or “1” in a particular category, instead of looking at individual questions and their respected frequencies. This was done because it allowed us to assess the quality of the study using the 4 main categories that encompass the individual questions. The Downs and Black tool\textsuperscript{116} is attached in Appendix F.

5.7 Meta-analysis

5.7.1 Summary Effect Size

All extracted outcomes were treated as continuous data. VA, measured as a logMAR value, and inflammation grade, measured on SUN’s grading scheme for anterior chamber cells and its variations, were reported as pre- and post-means. However, not many studies had pre- and post-inflammation grade on one scale that could be standardized, so we were unable to conduct a meta-analysis on inflammation grade. As discussed in Chapter 4 section 4.2.1, since the effect size was reported on a meaningful scale (logMAR), and all studies were converted to the same scale, we were able to perform a meta-analysis directly on the raw mean difference (D), rather than requiring a standardized mean difference (Cohen’s d). The explanation behind the computing of the raw mean score is that the scale is intuitively meaningful (ie, blood pressure, which is a known measurement scale, similar to logMAR for VA). Because the unit of analysis is the pair (ie, pre- and post-logMAR), the advantage of this design is that each pair serves as its own control, reducing the error term and increasing the statistical power. The calculations for the effect size and its variance were done via STATA, which required individual pre/post VA and pre/post SD data. So, it was important that all studies had the individual data in order for the analysis to be undertaken.

So, in studies where only the change in standard deviation and mean visual acuity were given, we imputed the data using the average pre-VA from the studies that had the data to
obtain the missing VA, and the post-VA was inferred using the change in VA that the particular study had provided.

To perform meta-analysis, both the pre- and post-VA and the individual standard deviation data was required for both pre- and post-means. When possible, missing VA and standard deviation data was computed using extracted raw data. However, when studies did not provide sufficient information for individual pre- and post-means and standard deviations, we had to impute the means and standard deviations for VA, keeping in the mind the change from pre-VA to post-VA was already calculated or provided, as was the SD.

With some studies, we knew the mean change, but did not know the specific pre- and post-values. Since these were required for meta-analysis, we imputed missing pre-visual acuity as an average of all available pre-data, then used change to infer post-data. We felt that using mean pre-data fairly estimated the visual acuity of patients prior to treatment, since the patients had similar conditions and could be used as an indicator of the visual acuity of patients prior to any treatment.

If a study did not include a change in standard deviation at all, and one could not be calculated with the raw data, then the Furukawa et al method was used for the missing pre- and post-SD. Furukawa et al (2006)\textsuperscript{118} showed that using imputed standard deviations from other studies in the same meta-analysis resulted in approximately correct results when compared to non-imputed (actual) standard deviations.\textsuperscript{4} We reviewed the possible standard deviation data from other included studies and imputed the highest pre-standard deviation as a conservative estimate for missing standard deviations. We recognized that this would lead to lower weighting of the study within the meta-analysis; however, we believed that to be a fair trade-off for its inclusion within the results rather than excluding the study if it did not include standard deviation.

5.7.2 Choice of Fixed vs. Random Effects Analysis

As discussed in section 4.2.4 of Chapter 4, meta-analysis was performed using a random effects model because we anticipated significant heterogeneity across studies. The
random effects model appropriately accounts for the differences in observed effects between studies that are beyond the expected heterogeneity due to sampling error alone. The studies ranged in areas such as participant mix (e.g., juvenile/senile, etc.) and prescribed treatment and dosage, leading to different possible true effect sizes. Therefore, we assumed that the reported raw mean differences were simply a random subset of all possible effect sizes and we assumed the effect sizes were normally distributed. The random effects model, using the DerSimonian and Laird method, determines the mean and standard deviation of this distribution, or in other words, the summary effect.

5.8 Sensitivity Analysis of Missing Data

We repeated the analysis while omitting studies that required imputed pre and post VA or standard deviations. If we saw changes, we checked for any change in heterogeneity; if none was found, the results were similar to the original analysis, so we reported the original analysis.

5.9 Heterogeneity

Heterogeneity between studies was visually assessed through paired forest plots.

As stated in section 4.2.5, to quantify the degree of statistical heterogeneity we used the Cochran Q (X2 test) and the Higgins I² statistic. Cochran Q allowed us to test the null hypothesis and obtain an estimate of the excess variance. The I² statistic is the proportion of observed dispersion that is real rather than spurious, and it is expressed as a ratio with a range of 0 to 100%. As a general rule, suggested by Cochrane an I² value of less than 25% is considered low heterogeneity; I² between 25 and 50% is moderate heterogeneity; and I² greater than 50% is high heterogeneity.¹¹⁹ However, as Higgins and Thompson (2002) noted there is no universal rule for the definition for mild, moderate and severe heterogeneity and that these suggestions are tentative.¹²⁰ So, care must be taken when concluding with I² and one should also consider size and direction of the effect alongside the I².¹²⁰,¹²¹
Once quantified, we explored potential sources of heterogeneity using subgroup analysis and meta-regression. We defined several patient and study characteristics as potential relevant subgroups and covariates. These are described in the following section.

5.9.1 Subgroup Analysis

As stated in the Cochrane handbook\textsuperscript{119}, it is important to note that our first meta-analysis is broad, examining the effect size of all the interventions together. However, this is similar to computing an effect size with apples and oranges, as the treatments are all different, and so a subgroup analysis was planned for the 3 main classes. A subgroup analysis can reduce the power, but it allows us to draw a more satisfactory conclusion.

Subgroup analysis was done by dividing the data into subgroups to indirectly identity if any heterogeneity was associated with any of the subgroups, or if there was positive change in logMAR due to any of the categories in the subgroup analysis. Because there were a limited number of studies in each subgroup, it was more appropriate to use a fixed effects model. Using a random effects model with subgroup analysis would yield poor precision, whereas the fixed effects model can be assumed to be accurate because the subgroups are expected to be homogenous.

5.9.1.1 Subgroup Analysis: Type of Immunosuppressive Treatment

To determine the individual effects of the different types of immunosuppressive treatment on logMAR, we assigned a value of 0 to 4 to each of the different types of treatment options, for analysis. The effects of individual treatment group on logMAR is important to understanding if a specific group had a more profound effect on logMAR, and ultimately on treating uveitis. The treatment types that were added were: antimetabolites (0), alkylating agents (1), T-lymphocytes inhibitors (2), steroid use only (3), or a combination of treatments (4).

5.9.1.2 Subgroup Analysis: Type of Primary Location

This analysis was used to determine the effects of the location of uveitis on logMAR. We assigned a value of 0 to 5 to each of the different types of location of uveitis options, for analysis. If there was a difference in the subgroups, it allowed us to draw conclusions
about which location responded better to immunosuppressive treatment. The different categories examined for the location of uveitis were: intermediate uveitis, posterior uveitis, panuveitis uveitis, not specified, or combination of the 2 or more of the locations in the study.

5.9.1.3 Subgroup Analysis: Previous Treatment

This analysis was used to determine whether any previous treatment that was administered to patients impacted the effectiveness the overall immunosuppressive treatment had on logMAR. We assigned a value of 0 to 2 to each of the different types of previous treatment options, for analysis. If there was a difference in the subgroups, it allowed us to draw conclusions about whether previous treatments affected the overall logMAR score (for better or worse) after patients were given the immunosuppressive treatment. The subgroups for previous treatments were: steroids only, not specified, or combination of steroids and immunosuppressive.

5.9.1.4 Subgroup Analysis: Average Patient Age

This analysis was used to determine if immunosuppressive treatment had differing effects on logMAR with regards to differences in the average age of patients. We assigned a value of 0 to 1 to each of the different types of age options, for analysis. If there was a difference in the subgroups, it allowed us to draw conclusions about which average age of patients was more positively affected by the treatment, if any. The subgroups for average age of patients were: either less than or equal to 18 years of average age (0), or greater than 18 (1). The reason we chose to stratify at 18 years of age is because pediatric uveitis and adult uveitis can be very different conditions, and thus evaluating whether a particular treatment is more effective in a younger or older age group is important.

Once the subgroup analysis was complete, we were able to compare the results using (1) the Z-test, (2) a Q-test for heterogeneity. If there were more than 2 subgroups, the Z-test was not used, as it is only used when comparing 2 groups. Instead, a Q-test was used to test the hypothesis.
5.9.2 Meta-regression

As discussed in Chapter 4, a meta-regression allows us to assess the relationship between different covariates and effect size.

In our study, most of the covariates were categories. In order to do this in Stata, dummy variables were coded and used for categorical univariate meta-regression, using the Knapp and Hartung (2003) method to take modifications to the variance into account, given our use of the random effects model. Thus, we used the t distribution instead of the normal distribution. In the Knapp and Hartung (2003) method of meta-regression, the restricted maximum likelihood is used to estimate the between-study component of variance. The restricted maximum likelihood was used over other methods, since it allows for greater caution when extrapolating the results for future patients or studies. This is because this method results in conservatively wide confidence interval of the estimated beta coefficient. We performed a t-test to assess the null hypothesis of no effect on logMAR for the different covariates discussed below. A p-value <0.05 (two-tailed) was considered statistically significant.

It is important to be aware of the issue of multiple comparisons, in which more than 2 covariates are compared and we want to measure the significance of each covariate (where the actual alpha may exceed the normal alpha). There is not much consensus as to which method should be used when dealing with this issue. One way is to conduct a joint test for all covariates, and obtain a p-value for the overall model, which would assess whether there is evidence for an association of any of the covariates with the outcome. However, when a small p-value indicates that there is evidence of that nature, it is hard to know which and how many of the covariates are implicated. Recently, some other methods have been established to examine the multiple comparison problems. One such method is to conduct the permutation test, developed by Higgins and Thompson (2004), to calculate the p-values, as described above. This test allows us to adjust for false positive findings when there are multiple covariates or variables, by using random permutations and comparing each t-statistic for every covariate with the largest t-statistic for any covariate in each random permutation.
So, in addition to the meta-regression for each of the covariates, we created dummy variables, and a univariate random effects model using the Higgins and Thompson (2004)\textsuperscript{108} permutation test was done to account for multiple testing.

The following covariates were used in the univariate random effects meta-regression to assess the impact of uveitis patients receiving immunosuppressive treatment on logMAR:

1) Location of Study: Even though there is no evidence that the practice in North America is different from other continents and countries, a meta-regression on the location of study was still done. One category was North America; the other was any other location included in the study.

2) Year of Publication: We abstracted the year the study was published. Even though there was no change in practice before or after 2005, we still conducted a meta-regression. 2005 was chosen because that was the year the SUN classification was published, and we speculated that there could be a difference in the studies due to that publication. There were 2 categories, 1 for studies conducted after 2005 and 1 for studies conducted before.

3) Type of Study: Comparing studies that were observational to RCTs. This was to understand whether the type of study affects the quality of study, and a change in logMAR.

4) Sex: We modelled sex distribution based on the percentage of females in the study population.

5) Mean Age: Mean age was dichotomous, with patients divided into those younger than 18 and those equal to or older than 18.

6) Location of Disease: There were 5 categories for location of disease: a) intermediate uveitis, b) posterior uveitis, c) panuveitis uveitis, d) not specified, or e) combination of the 2 or more of the locations in the study.
7) Previous Treatment: There were 3 categories for previous treatments given to patients: a) steroids only, b) not specified, or c) combination of steroids and immunosuppressives.

8) Primary Treatment: There were 5 categories for the primary treatment given to patients: a) antimetabolites, b) alkylating agents, c) T-lymphocytes inhibitors, d) steroid use, or e) a combination of treatments.

A permutation test with 5000 permutations on the covariates p-value was conducted to alleviate any false negatives that may have been present due to multiplicity.

5.10 Publication Bias

Publication bias could have a pronounced effect on the results of our study, as some studies could have been missed in our screening phases. This could result in less information, wider confidence intervals, and less powerful tests. There could be bias due to larger studies being included and smaller studies being excluded, because they are not as easy to find. One method to manage publication bias is to use random effects model, which ensures that all the studies are evenly weighted, but that does not take into account how much publication bias may exist or how the data would look if those studies were not missing. Other methods have been developed to determine if publication bias has in fact taken place, and some methods can even adjust for the bias. These methods use a funnel plot to identify any asymmetry. To determine whether the asymmetry is due to chance, there are tests, such as Begg and Mazumdar (1994)\textsuperscript{109} and Egger et al (1997)\textsuperscript{110}. However, these methods do not provide estimates of the number or characteristics of the missing studies, nor do they provide an estimate of the underlying (unbiased) effect.

Duval and Tweedie (2000)\textsuperscript{111} developed the Trim and Fill method to estimate adjusted effect size, and that is what we used to assess publication bias in our study. The Trim and Fill method works by removing small studies (trimming), which yields a publication bias-adjusted effect size. Because this trimming underestimates the variance, the studies are then added back with an imputing mirror study (filling), such that the funnel plots
become symmetrical and the variance is corrected. This allows us not only assess the presence of publication bias, but also to measure its impact on the observed effect size.

5.11 Software

For systematic review and meta-analysis, we used EPPI version 4.3 (EPPI Centre, Institute of Education, London, UK; 2013)\textsuperscript{124} as our reference management program, used for collection, sorting and screening. Statistical analysis was performed using STATA 13 (Stata Corp, Austin, TX USA). In STATA special codes were used to do the random effects meta-analysis (metan, with specification to use the random effects model). For the meta-regression using the Knapp and Hartung (2003)\textsuperscript{107} method, we used the metreg command. With the publication bias, the metatrim command was used.
Chapter 6

6 Results

6.1 Study Selection

Upon completion of the database search, 2215 articles were included from the databases and grey literature. No articles were added after extensive snowballing and the grey literature search. After removing duplicate records, there were 1518 unique articles for level 1 screening. After level 1 screening was complete, 1248 articles were removed (kappa for the 2 independent reviewers was 0.89; 95% confidence interval 0.81 to 0.94). Most articles that were removed during level 1 screening were review articles (over >80% of the removed articles), biologic treatment (which are not relevant to the study question), animal studies and/or surgical procedures. The remaining 270 articles were considered for full article review (ie, level 2).

After level 2, 45 articles satisfied the inclusion criteria (kappa for the 2 independent reviewers was 0.72; 95% confidence interval 0.65 to 0.79). The 225 excluded articles were removed for the following reasons: Not English (n=29), fewer than 5 patients (n=19), location of disease (n=20), not idiopathic uveitis (n=31), other diseases (n=54), not in humans (n=2), not oral treatment (n=17), not primary article (n=34), not the outcome considered (n=9), not the treatment considered or not specific enough (n=6), missing articles (n=4). All of the total 45 studies were used for descriptive outcomes, however, only 26 articles had sufficient data for the purpose of conducting a meta-analysis. Figure 3 showcases the Prisma diagram that details the selection process.
Figure 3: Prisma Diagram

Records identified through database searching  
(n = 2215)

Records after duplicates removed  
(n = 1518)

Records screened  
(n = 1518)

Records excluded  
(n = 1248)

Full-text articles assessed for eligibility  
(n = 270)

Studies included in qualitative synthesis  
(n = 45)

Studies included in quantitative synthesis  
(meta-analysis)  
(n = 26)

Due to independent subgroups within individual studies  
(n=32)

Full-text articles excluded from systematic review, with reasons  
(n = 225)

- Not English (n=29)
- Less than 5 patients  
(n=19)
- Location of disease  
(n=20)
- Not idiopathic uveitis  
(n=31)
- Other diseases (n=54),  
- Not in humans (n=2)
- Not oral treatment (n=17)  
- Not primary article  
(n=34)
- Not the outcome considered (n=9)
- Not the treatment considered or not specific enough (n=6)
- Missing articles (n=4)

Full text articles removed from meta-analysis  
(n= 19)

- Did not have the pre and post VA data  
(n=19)
6.2 Treatment Categories

Of the 45 studies that were included in the systematic review, the antimetabolites treatment group consisted of 23 studies, which broke down further to specific treatments, with 12 studies for MMF, followed by 9 studies for MTX, and 2 studies for AZA. All of these treatments were treating mostly idiopathic uveitis patients (77.6% of the patients from the studies specifically had idiopathic uveitis). Also, important to note most studies presented results on the patient level either with subjects or with eyes.

Sixteen studies fell within the inhibitors of T-lymphocyte signalling treatment group, which broke down to 12 studies for CsA, 3 studies for TAC, and only 1 study that examined both TAC and CsA. Only 1 study used the alkylating agent, Chlorambucil. There were 2 studies that looked at multiple treatment groups; BenEzra et al examined Chlorambucil, AZA and CsA, while Dick et al examined CsA, or CsA plus AZA. There were 3 studies that examined various combined immunosuppressive treatments. This is summarized in Table 10.

Table 10: Number of studies for each treatment category

<table>
<thead>
<tr>
<th>Treatment Class</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites (n=23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azathioprine (n=2)</td>
</tr>
<tr>
<td></td>
<td>Methotrexate (n=9)</td>
</tr>
<tr>
<td></td>
<td>Mycophenolate Mofetil (n=12)</td>
</tr>
<tr>
<td>Alkylating Agents (n=1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorambucil (n=1)</td>
</tr>
<tr>
<td>Inhibitors of t-lymphocyte signaling (n=16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclosporine (n=12)</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus (n=3)</td>
</tr>
<tr>
<td>Multiple Treatment Groups (n=2)</td>
<td>--</td>
</tr>
<tr>
<td>Combined Immunosuppressive Treatment (n=3)</td>
<td>--</td>
</tr>
</tbody>
</table>
6.2.1 Inhibitors of T-lymphocyte signalling

6.2.1.1 Cyclosporine A

6.2.1.1.1 Study Characteristics

Twelve studies reported solely on CsA. Seven studies were conducted in the USA, 2 in Canada, and 3 in the UK. Studies were conducted between 1979 and 2010.

The study designs included: One study was an RCT, 7 studies were prospective cohort studies, 2 studies were retrospective cohort studies, and 2 studies were retrospective case series. The total sample size was 711. Study characteristics are summarized in Table 1 on the following page.

6.2.1.1.2 Study Size and Patient Characteristics

Two studies included patients <16 years of age (Kilmartin et al (1998)\textsuperscript{125} had patients with an average age of 8.7, while Walton et al (1997)\textsuperscript{126} had patients aged around 12.9). In all the other studies, the mean age ranged from 34 to 49 years. Ten of 12 studies provided gender proportions ranging from 29-63% female. Reported follow up time ranged from 3 to 227 months, with 2 studies not reporting any follow up. Cause of uveitis was mainly uveitis with 7 of the 12 studies, where 100% of the patient’s uveitis was idiopathic in nature. Uveitis type was classified as intermediate in 4 studies, non-classified in 3 studies, posterior in 2 studies, and mixed in the remaining studies. Six studies had steroid usage, 2 had steroid combined with immunosuppressive, 1 used immunosuppressive treatment exclusively, and 3 used no oral drugs. Table 12 presents a summary of the patient characteristics.

6.2.1.1.3 Descriptive Outcomes

Eight studies did not report how many patients experienced improvement to or maintained VA. Four studies mentioned frequency of patients that got better, of which, Walton et al showed 82.1% of patients improved or maintained VA, and Kilmartin et al (1998)\textsuperscript{125} showed that 92% of patients had improved or maintained VA. Leznoff et al (1992)\textsuperscript{127} reported only 20% of patients improving or maintaining VA, while Rocha et al
(1997)\textsuperscript{128} showed 43.75\% of patients improving or maintaining VA. Three studies reported the frequency of patients that had maintained or improved inflammation grade. Kacmaz et al (2010)\textsuperscript{129} reported improvement in inflammation grade in 51.9\% of patients overall, ranging from 45.5\% to 58.5\%. The second study reported that 76\% of patients had maintained or improved inflammation grade, and the third study reported that 49\% of patients had improved or maintained inflammation grade.

\subsection*{6.2.1.1.4 Reason for Discontinuation and Adverse Events}

Four studies reported cases of treatment discontinuation due to intolerance (ie, side effects). In Palestine et al (1985)\textsuperscript{130}, about 30\% of patients had to discontinue due to intolerance. In Rosales (2011)\textsuperscript{131}, 11\% of patients had to discontinue because of intolerance. In Kacmaz (2010)\textsuperscript{129}, renal toxicity was a cause of discontinuation in 4.3\% of patients, while side effects in general were the cause of discontinuation in 11.1\% of patients in Kilmartin et al (1998)\textsuperscript{125}, and within the same study 11.1\% of patients discontinued due to the treatment being ineffective.

Nephrotoxicity was the primary adverse events mentioned in 2 studies. 80\% of patients in 1 study experienced nephrotoxicity, and 31.3\% of patients experienced it in the other. Hypertension was the primary adverse event mentioned in 4 studies, ranging from 19-80\% of patients afflicted. Other adverse events included tremors (40\%), increased creatinine levels (28\%), and digestive intolerance in 38\% of patients. Table 13 summarizes the descriptive outcomes, including the adverse events.
Table 11: Cyclosporine A Treatment, Study Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Design</th>
<th>Setting/Data source</th>
<th>Accrual Period</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derary et al, 1992132</td>
<td>PCS</td>
<td>France</td>
<td>1986 to 1990</td>
<td>16</td>
</tr>
<tr>
<td>Isnard et al, 2002133</td>
<td>PCS</td>
<td>France</td>
<td>April 1986 to December 1997</td>
<td>41</td>
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<tr>
<td>Leznoff et al, 1992127</td>
<td>PCS</td>
<td>Canada</td>
<td>1987</td>
<td>18</td>
</tr>
<tr>
<td>Rubin et al, 1993134</td>
<td>PCS</td>
<td>USA</td>
<td>--</td>
<td>32</td>
</tr>
<tr>
<td>Palestine et al, 1985130</td>
<td>PCS</td>
<td>USA</td>
<td>--</td>
<td>60</td>
</tr>
<tr>
<td>Rosales et al*, 2011131</td>
<td>RCS</td>
<td>USA</td>
<td>January 1992 to October 2010</td>
<td>--</td>
</tr>
<tr>
<td>Walton et al, 1997126</td>
<td>RCaseS</td>
<td>USA</td>
<td>1983 to 1993</td>
<td>75</td>
</tr>
<tr>
<td>Rocha et al, 1997128</td>
<td>PCS</td>
<td>Canada</td>
<td>August 1992 to January 1995</td>
<td>8</td>
</tr>
<tr>
<td>Kacmaz et al, 2010129</td>
<td>RCS</td>
<td>USA</td>
<td>1979 and 2007</td>
<td>62</td>
</tr>
<tr>
<td>Kilmartin et al, 1998125</td>
<td>RcaseS</td>
<td>UK</td>
<td>--</td>
<td>373</td>
</tr>
<tr>
<td>Nussenblatt et al, 1985135</td>
<td>PCS</td>
<td>USA</td>
<td>--</td>
<td>14</td>
</tr>
<tr>
<td>Ramadan et al, 1996136</td>
<td>Double-masked, RCT</td>
<td>USA</td>
<td>--</td>
<td>12</td>
</tr>
</tbody>
</table>

Legend: RCaseS= retrospective case series, RCS= retrospective cohort study, PCS= Prospective cohort study *= abstract
### Table 12: Cyclosporine A Treatment, Patient Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Mean Age</th>
<th>Age SD</th>
<th>% Female</th>
<th>Mean Follow-up (Mo.)</th>
<th>Mean Follow-up SD</th>
<th>Prim Cause</th>
<th>%</th>
<th>Location of disease</th>
<th>%</th>
<th>Previous Treatment</th>
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<tr>
<td>Derary et al, 1992132</td>
<td>45.6</td>
<td>2.7</td>
<td>56</td>
<td>24</td>
<td>--</td>
<td>Idio</td>
<td>100</td>
<td>Int or Pos</td>
<td>100</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Isnard et al, 2002133</td>
<td>49</td>
<td>10</td>
<td>56</td>
<td>55.4</td>
<td>0.2</td>
<td>Idio</td>
<td>100</td>
<td>Pos</td>
<td>100</td>
<td>None</td>
</tr>
<tr>
<td>Leznoff et al, 1992127</td>
<td>45</td>
<td>13.5</td>
<td>40</td>
<td>--</td>
<td>--</td>
<td>Idio</td>
<td>100</td>
<td>--</td>
<td></td>
<td>Prednisone</td>
</tr>
<tr>
<td>Rubin et al, 1993134</td>
<td>33.8</td>
<td>--</td>
<td>62.5</td>
<td>14</td>
<td>--</td>
<td>Idio</td>
<td>59.4</td>
<td>Pos, Int, and Pan</td>
<td>46.9</td>
<td>Prednisone</td>
</tr>
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<td>16.8</td>
<td>--</td>
<td>3</td>
<td>--</td>
<td>Idio</td>
<td>100</td>
<td>Int</td>
<td>100</td>
<td>--</td>
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<tr>
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<td>54.7</td>
<td>226.8</td>
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<td>NAU</td>
<td>100</td>
<td>--</td>
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<td>--</td>
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<tr>
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<td>2.5</td>
<td>46.7</td>
<td>44.5</td>
<td>7.3</td>
<td>CU</td>
<td>100</td>
<td>Int</td>
<td>47</td>
<td>Prednisone</td>
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<tr>
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<td>14</td>
<td>62.5</td>
<td>16</td>
<td>10</td>
<td>Idio</td>
<td>75</td>
<td></td>
<td></td>
<td>Corticosteroids/azathioprine resistant</td>
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<tr>
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<td>36.1</td>
<td>19</td>
<td>62.7</td>
<td>10.8</td>
<td>--</td>
<td>Idio</td>
<td>92.4</td>
<td>Pos or Int</td>
<td>45.8</td>
<td>Prednisone+Immunosuppressive</td>
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<td>8.7</td>
<td>12.4</td>
<td>28.6</td>
<td>26.8</td>
<td>21.2</td>
<td>PP</td>
<td>55.7</td>
<td>Int</td>
<td>57.1</td>
<td>Systemic steroids</td>
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<td>Idio</td>
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<td>Int</td>
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<td>--</td>
<td>13.3</td>
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</tbody>
</table>

**Legend:** SD= Standard Deviation, a= CsA with Ketoconazole, Idio= Idiopathic, NAU= Non-infectious autoimmune uveitis, CU= Chronic uveitis, PP= Pars Planitis, Pos= Posterior, Int= Intermediate, Pan= Panuveitis, *= Abstract
Table 13: Cyclosporine A Treatment, Descriptive Outcomes

<table>
<thead>
<tr>
<th>Citation</th>
<th>IMVA</th>
<th>IMI</th>
<th>Discontinuation Reason</th>
<th>Prim. reason</th>
<th>%</th>
<th>Sec. reason</th>
<th>%</th>
<th>Adverse events prim.</th>
<th>%</th>
<th>Adverse events sec.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derary et al, 1992132</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Nephrototoxic</td>
<td>80</td>
<td>Hypertension</td>
<td>80</td>
</tr>
<tr>
<td>Isnard et al, 2002133</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Leznoff et al, 1992127</td>
<td>20</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Increased hypertension</td>
<td>20</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Rubin et al, 1993134</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Renal toxicity</td>
<td>31.25</td>
<td>Hypertension</td>
<td>18.75</td>
</tr>
<tr>
<td>Palestine et al, 1985130</td>
<td>--</td>
<td>49</td>
<td>Intolerance</td>
<td>30</td>
<td>--</td>
<td>P</td>
<td>Parasthesia</td>
<td>--</td>
<td>Gastrointestinal distress</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Rosales et al*, 2011131</td>
<td>--</td>
<td>--</td>
<td>Intolerance</td>
<td>11</td>
<td>--</td>
<td>--</td>
<td>Digestive intolerance</td>
<td>38</td>
<td>Increase of creatinine level</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Walton et al, 1997126</td>
<td>82.1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Increases in serum creatinine</td>
<td>53</td>
<td>Hyperplasia</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Rocha et al, 1997128</td>
<td>43.8</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Tremor</td>
<td>0.4</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Kacmaz et al, 2010129</td>
<td>--</td>
<td>51.9</td>
<td>Side effects</td>
<td>Renal toxicity</td>
<td>4.3</td>
<td>Hypertension</td>
<td>3.2</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>21</td>
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<tr>
<td>Kilmartin et al, 1998125</td>
<td>92</td>
<td>76</td>
<td>--</td>
<td>Side effects</td>
<td>11.1</td>
<td>Ineffective</td>
<td>11.1</td>
<td>Hypertrichosis</td>
<td>29</td>
<td>Fatigue</td>
<td>--</td>
</tr>
<tr>
<td>Nussenblatt et al, 1985135</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Ramadan et al, 1996136</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Legend: IMVA= Improving or maintaining Visual Acuity, IMI= Improving or maintaining Inflammation, Prim Reason= Primary, Sec= Secondary, %= Frequency of patients, *= Abstract
6.2.1.2 Tacrolimus

6.2.1.2.1 Study Characteristics

There were 3 studies that had administered TAC to patients as the main treatment. Two of these were conducted in the UK, while location was not specified in the other. The studies were conducted between 2004 and 2009. The designs of the 3 studies were as follow: 1 RCT, 1 retrospective case series, and 1 prospective cohort study. The RCT compared steroid and TAC usage to TAC with steroids. The total sample size was 61. Study characteristics are summarized in Table 14.

6.2.1.2.2 Study Size and Patient Characteristics

The mean age in the studies ranged from 38 to 40.6 years. The RCT with TAC and steroid use had an average age of 31.3 years. The gender proportions ranged from 50-90.9% females. Only 1 study reported follow up time, which was 45 months. The cause of uveitis was idiopathic in 67% of the patients. Uveitis type was classified as intermediate in 1 study and posterior in the other 2 studies, where 1 reported all patients as posterior, and the other 37.1%. One study only had prior steroids usage, while another study had both prior steroids and CsA usage, and the last 1 had prior steroid and other immunosuppressive treatments. Patient characteristics are summarized in Table 15.

6.2.1.2.3 Descriptive Outcomes

Of the 3 studies, only Figueroa et al (2007)\textsuperscript{137} mentioned the percentage of patients who improved or maintained VA and inflammation grade. With 80.95% of patients improved or maintained VA and 54.5% of patients improved or maintained in inflammation grade.

6.2.1.2.4 Reason for Discontinuation and Adverse Events

With the RCT, TAC + steroids, treatment failure accounted for 50% of patients discontinuing the treatment, while with just TAC in the RCT, 100% of the patients had to discontinue.
Lack of efficacy was the cause of discontinuation for the other 2 studies, which accounted for 36.4% and 24.2% of patients having to discontinue the treatment, respectively.

In the RCT, 12.5% of the patient population experienced cramps, and 10.5% experienced tremors with TAC and steroids in the RCT. Tremors and headaches were the main adverse events in patients of the other 2 studies, with 72.7% of patients experiencing hand tremors in Figueroa et al. In addition, 54.5% of patients in Figueroa et al experienced headaches. Descriptive outcomes, including the adverse events, are summarized in Table 16.

Table 14: Tacrolimus Treatment, Study Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Design</th>
<th>Setting/Data source</th>
<th>Accrual Period</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee Richard et al, 2012\textsuperscript{138}</td>
<td>Steroid + Tacrolimus</td>
<td>RCT*</td>
<td>UK</td>
<td>May 2004 to January 2009</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td></td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Figueroa et al, 2007\textsuperscript{137}</td>
<td>Tacrolimus</td>
<td>PCS</td>
<td>--</td>
<td>November 2000 to November 2005</td>
<td>15</td>
</tr>
<tr>
<td>Hogan et al, 2007\textsuperscript{139}</td>
<td>Tacrolimus</td>
<td>RCS</td>
<td>Bristol Eye Hospital, United Kingdom</td>
<td>April 2000 and April 2004</td>
<td>11</td>
</tr>
</tbody>
</table>

Legend: RCT* = Randomized, controlled, phase 2b, open-label, dual-center no inferiority trial, PCS= Prospective Cohort Study, RCS= Retrospective Case Series
### Table 15: Tacrolimus Treatment, Patient Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Mean Age</th>
<th>Age SD</th>
<th>%Female</th>
<th>Mean Follow-up (Mo.)</th>
<th>Mean Follow-up SD</th>
<th>Prim. Cause</th>
<th>%</th>
<th>Location of disease</th>
<th>%</th>
<th>Previous Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee Richard et al, 2012&lt;sup&gt;138&lt;/sup&gt;</td>
<td>Steroid + Tacrolimus</td>
<td>31.3</td>
<td>--</td>
<td>52.6</td>
<td>--</td>
<td>--</td>
<td>Idio</td>
<td>63.2</td>
<td>Int</td>
<td>42</td>
<td>Prednisone</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td>39.8</td>
<td>--</td>
<td>50</td>
<td>--</td>
<td>--</td>
<td>Idio</td>
<td>68.9</td>
<td>Int</td>
<td>62.5</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Figueroa et al, 2007&lt;sup&gt;137&lt;/sup&gt;</td>
<td>Tacrolimus</td>
<td>40.6</td>
<td>14.7</td>
<td>90.9</td>
<td>45</td>
<td>11.3</td>
<td>Idio</td>
<td>63.6</td>
<td>Pos</td>
<td>100</td>
<td>Pred+CsA</td>
</tr>
<tr>
<td>Hogan et al, 2007&lt;sup&gt;139&lt;/sup&gt;</td>
<td>Tacrolimus</td>
<td>38</td>
<td>13.8</td>
<td>72.5</td>
<td>--</td>
<td>--</td>
<td>Idio</td>
<td>70.96</td>
<td>Pos</td>
<td>37.1</td>
<td>Pred+ immuno suppressive</td>
</tr>
</tbody>
</table>

**Legend:** Idio= Idiopathic, Pos= Posterior, Int= Intermediate, Pred = Prednisone, %= Frequency of patients

### Table 16: Tacrolimus Treatment, Descriptive Outcomes

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>IMVA</th>
<th>IMI</th>
<th>Reason for discontinuation</th>
<th>Primary reason</th>
<th>%</th>
<th>Primary Adverse events</th>
<th>%</th>
<th>Secondary Adverse events</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee Richard et al, 2012&lt;sup&gt;138&lt;/sup&gt;</td>
<td>Steroid + Tacrolimus</td>
<td>--</td>
<td>--</td>
<td>Treatment failure: 50% due to drug intolerance</td>
<td>Intolerance</td>
<td>50</td>
<td>Cramp</td>
<td>12.5</td>
<td>Tremor</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td>--</td>
<td>--</td>
<td>Disease Failure: 100% due to disease reactivation</td>
<td>Lack of efficacy</td>
<td>100</td>
<td>Cramp</td>
<td>12.5</td>
<td>Tremor</td>
<td>6.3</td>
</tr>
<tr>
<td>Figueroa et al, 2007&lt;sup&gt;137&lt;/sup&gt;</td>
<td>Tacrolimus</td>
<td>80.95</td>
<td>54.5</td>
<td>Efficacy</td>
<td>Efficacy</td>
<td>36.4</td>
<td>Hand tremor</td>
<td>72.7</td>
<td>Headache</td>
<td>54.5</td>
</tr>
<tr>
<td>Hogan et al, 2007&lt;sup&gt;139&lt;/sup&gt;</td>
<td>Tacrolimus</td>
<td>--</td>
<td>--</td>
<td>Efficacy</td>
<td>Efficacy</td>
<td>24.2</td>
<td>Tremor</td>
<td>8.06</td>
<td>Headache</td>
<td>6.45</td>
</tr>
</tbody>
</table>

**Legend:** IMVA= Improving or maintaining Visual Acuity, IMI= Improving or maintaining Inflammation, %= Frequency of patients
6.2.1.3  Tacrolimus or Cyclosporine

6.2.1.3.1  Study Characteristics

One study compared TAC to CsA in a prospective RCT, which was conducted in the UK between 2001 and 2003. Study characteristics are summarized in Table 17.

6.2.1.3.2  Study Size and Patient Characteristics

In this study, 19 patients were administered TAC and 18 patients were administered CsA. The average age of the patients that were given TAC was 48 years, while the average age for patients that were given CsA was 38 years. 58% of female patients were given TAC and 56% of female patients were given CsA. The mean follow up for the TAC patients was 7 months, and it was 4 months for CsA patients. Idiopathic uveitis made up 53% of the patients that were given CSA, and 57% that were given TAC. All 3 locations were treated in this study. The previous treatment used in this study was steroids. Patient characteristics are summarized in Table 18.

6.2.1.3.3  Descriptive Outcomes

The post-VA was maintained or improved in 68% of the patients given TAC and in 67% of the patients given CsA.

6.2.1.3.4  Reason for Discontinuation and Adverse Events

No mention of discontinuation of treatment was discussed. However, adverse events were reported for both CsA and TAC. The main adverse events for patients treated with CsA were fatigue at 56%, and tremors, which occurred in 44% of patients. 37% of the patients given TAC had paresthesia, and 32% of patients developed tremors after being given TAC. Descriptive outcomes, including the adverse events, are summarized in Table 19.
Table 17: Tacrolimus or Cyclosporine A Treatment, Study Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Design</th>
<th>Setting/Data source</th>
<th>Accrual Period</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy et al, 2005</td>
<td>Tac</td>
<td>Prospective randomized trial</td>
<td>United Kingdom (Bristol Eye Hospital [Bristol, England] and Aberdeen Royal Infirmary [Aberdeen, Scotland])</td>
<td>May 2001 and April 2003</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>CsA</td>
<td></td>
<td></td>
<td></td>
<td>18</td>
</tr>
</tbody>
</table>
Table 18: Tacrolimus or Cyclosporine A Treatment, Patient Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Mean Age</th>
<th>Age SD</th>
<th>%Female</th>
<th>Mean Follow-up (Mo.)</th>
<th>Mean Follow-up SD</th>
<th>Prim. Cause</th>
<th>%</th>
<th>Location of disease</th>
<th>%</th>
<th>%</th>
<th>Previous Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy et al, 2005&lt;sup&gt;1-2&lt;/sup&gt;</td>
<td>TAC</td>
<td>48</td>
<td>4.8</td>
<td>58</td>
<td>7</td>
<td>3.5</td>
<td>Idio</td>
<td>57</td>
<td>Posterior, intermediate and panuveitis</td>
<td>100</td>
<td>74</td>
<td>Prednisone</td>
</tr>
<tr>
<td></td>
<td>CsA</td>
<td>38</td>
<td>6</td>
<td>56</td>
<td>4</td>
<td>2.5</td>
<td>Idio</td>
<td>53</td>
<td>Posterior, intermediate and panuveitis</td>
<td>100</td>
<td>78</td>
<td>Prednisone</td>
</tr>
</tbody>
</table>

**Legend:** Idio = Idiopathic, Pos = Posterior, Int = Intermediate, Pred = Prednisone

Table 19: Tacrolimus or Cyclosporine A Treatment, Descriptive Outcomes

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>IMVA</th>
<th>Primary Adverse event</th>
<th>%</th>
<th>Secondary Adverse events</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy et al, 2005&lt;sup&gt;1-2&lt;/sup&gt;</td>
<td>TAC</td>
<td>68</td>
<td>Paraesthesia</td>
<td>37</td>
<td>Tremors</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>CsA</td>
<td>67</td>
<td>Fatigue</td>
<td>56</td>
<td>Tremors</td>
<td>44</td>
</tr>
</tbody>
</table>

**Legend:** IMVA = Improving or maintaining Visual Acuity, % = Frequency of patients
6.2.2 Antimetabolites

6.2.2.1 Mycophenolate Mofetil

6.2.2.1.1 Study Characteristics

Studies that administered MMF for uveitis were conducted in Germany (n= 5), other parts of Europe (n=3), and the USA (n=4). The studies collected patient data from as early as 1995, and the latest data was collected at the end of 2007. Four studies did not provide an accrual period. The full paper could not be attained for 1 study (Capriotti et al\textsuperscript{18}). Eight studies were retrospective case series, 3 were cohort studies, of which 2 studies were prospective cohort studies and 1 was a retrospective cohort study. Study characteristics are summarized in Table 20.

6.2.2.1.2 Study Size and Patient Characteristics

The total sample size for the MMF studies was 607. The mean age of the patients that were given MMF across the studies ranged from 8 to 57.3 years. Most studies had a mean age in the 40s, while 1 study that looked at juvenile idiopathic patients had a mean age of 8 years. In most studies, females accounted for about 50% of the patient population (ranging from 33% to 68.8%). Mean follow up time reported ranged from 21.4 months to 69.7 months, with 1 study not reporting. One study considered patients with panuveitis, while the other 10 looked at idiopathic uveitis. There was an average of 73% of idiopathic uveitis patients.

Uveitis type was classified as intermediate in 4 studies, as mixed posterior and intermediate in 1 study, and was non-classified in 2 studies. One study divided their patient population by location of disease, so they had patients with posterior uveitis (n= 23), intermediate uveitis (n=53), and panuveitis (n=6). Five studies had prior steroid usage, 4 had steroid with immunosuppressive treatment and 1 used immunosuppressive treatment exclusively. Patient characteristics are summarized in Table 21.
6.2.2.1.3 Descriptive Outcomes

One measure of effectiveness used was the frequency of patients for whom VA was improved or maintained. Ten studies demonstrated that MMF was effective in treating patients, with 76.3% to 94.7% of patients having maintained or improved VA, and with 2 studies not reporting. Seven studies had improvement to inflammation grade, with a range of 60.9% to 94.2%, with 5 studies not reporting.

6.2.2.1.4 Reason for Discontinuation and Adverse Events

Five studies indicated that MMF was discontinued in 12-35% of patients due to lack of efficacy. Another 5 studies indicated that lack of efficacy was the most common adverse effect in patients with MMF use. The secondary adverse event that was quite common was fatigue. Descriptive outcomes, including the adverse events, are summarized in Table 22.
Table 20: Mycophenolate Mofetil Treatment, Study Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Design</th>
<th>Setting/Data source</th>
<th>Accrual Period</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capriotti et al, 2005*141</td>
<td>MMF</td>
<td>RCaseS</td>
<td>USA</td>
<td>--</td>
<td>41</td>
</tr>
<tr>
<td>Bhat et al, 2009142</td>
<td>MMF</td>
<td>RCaseS</td>
<td>Massachusetts Eye Research and Surgery Institute</td>
<td>2005 to 2007</td>
<td>7</td>
</tr>
<tr>
<td>Neri et al, 2009143</td>
<td>MMF</td>
<td>RCaseS</td>
<td>The Eye Clinic of the Polytechnic University of Marche</td>
<td>2003 to 2007</td>
<td>19</td>
</tr>
<tr>
<td>Benson et al, 2006144</td>
<td>MMF</td>
<td>RCaseS</td>
<td>Bristol Eye Hospital’s Regional Ocular Inflammatory Service, United Kingdom</td>
<td>2000 to 2006 (consecutive 100 patients)</td>
<td>100</td>
</tr>
<tr>
<td>Daniel et al, 2010145</td>
<td>MMF</td>
<td>RCS</td>
<td>USA</td>
<td>1995 to 2007</td>
<td>236</td>
</tr>
<tr>
<td>Deuter et al, 2009146</td>
<td>Mycophenolate sodium</td>
<td>RCaseS</td>
<td>Germany</td>
<td>--</td>
<td>35</td>
</tr>
<tr>
<td>Doycheva et al, 2012147</td>
<td>MMF</td>
<td>RCaseS</td>
<td>Germany</td>
<td>--</td>
<td>38</td>
</tr>
<tr>
<td>Zierhut et al, 2011148</td>
<td>MMF</td>
<td>RCaseS</td>
<td>Germany</td>
<td>--</td>
<td>60</td>
</tr>
<tr>
<td>Stuebiger et al, 2007149</td>
<td>MMF</td>
<td>RCaseS</td>
<td>Germany</td>
<td>2000 to 2005</td>
<td>17</td>
</tr>
<tr>
<td>Forrester et al, 1998150</td>
<td>MMF</td>
<td>RCS</td>
<td>Aberdeen Royal Hospitals, Scotland</td>
<td>--</td>
<td>9</td>
</tr>
<tr>
<td>Siepmann et al, 2006151</td>
<td>MMF</td>
<td>PCS</td>
<td>Germany</td>
<td>Between 1998 and 2003</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>MMF</td>
<td>PCS</td>
<td>Germany</td>
<td>Between 1998 and 2003</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>MMF</td>
<td>PCS</td>
<td>Germany</td>
<td>Between 1998 and 2003</td>
<td>6</td>
</tr>
<tr>
<td>Llinares-Tello et al, 2004152</td>
<td>MMF</td>
<td>PCS</td>
<td>USA</td>
<td>--</td>
<td>12</td>
</tr>
</tbody>
</table>

Legend: RCaseS= Retrospective Case series, RCS= Retrospective Cohort Study, PCS= Prospective Cohort Study, *=abstract
<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Mean Age</th>
<th>Age SD</th>
<th>%Female</th>
<th>Mean Follow-up (Mo.)</th>
<th>Mean Follow-up SD</th>
<th>Prim. Cause</th>
<th>% Location of disease</th>
<th>% Previous Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capriotti et al, 2005</td>
<td>MMF</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>26.8</td>
<td>--</td>
<td>Idio</td>
<td>100</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Bhat et al, 2009</td>
<td>MMF</td>
<td>49</td>
<td>17.25</td>
<td>57</td>
<td>39.6</td>
<td>9.6</td>
<td>Panuveitis</td>
<td>100</td>
<td>Immunomodulatory</td>
</tr>
<tr>
<td>Neri et al, 2009</td>
<td>MMF</td>
<td>32.9</td>
<td>8.9</td>
<td>42.8</td>
<td>30</td>
<td>6</td>
<td>Idio</td>
<td>56.3</td>
<td>Steroids, CsA, AZA, MTX</td>
</tr>
<tr>
<td>Benson et al, 2006</td>
<td>MMF</td>
<td>39</td>
<td>14.3</td>
<td>65</td>
<td>24</td>
<td>4.75</td>
<td>Idio</td>
<td>61</td>
<td>Pos and Int</td>
</tr>
<tr>
<td>Daniel et al, 2010</td>
<td>MMF</td>
<td>47.1</td>
<td>19.0</td>
<td>64</td>
<td>21.6</td>
<td>4.5</td>
<td>Idio</td>
<td>100</td>
<td>Int and Pos</td>
</tr>
<tr>
<td>Deuter et al, 2009</td>
<td>MMF</td>
<td>42.7</td>
<td>14.5</td>
<td>62.8</td>
<td>68.8</td>
<td>9.6675</td>
<td>Idio</td>
<td>77.1</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Doycheva et al, 2012</td>
<td>MMF</td>
<td>42.42</td>
<td>17</td>
<td>68.8</td>
<td>69.7</td>
<td>61.5</td>
<td>Idio</td>
<td>71.1</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Zierhut et al, 2011</td>
<td>MMF</td>
<td>40</td>
<td>17.8</td>
<td>61.7</td>
<td>71</td>
<td>4.5</td>
<td>Idio</td>
<td>61.7</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Stuebiger et al, 2007</td>
<td>MMF</td>
<td>8</td>
<td>2.8</td>
<td>41.2</td>
<td>36</td>
<td>13.75</td>
<td>Idio</td>
<td>64.7</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Forrester et al, 1998</td>
<td>MMF</td>
<td>39.5</td>
<td>--</td>
<td>78.9</td>
<td>72.7</td>
<td>9</td>
<td>Idio</td>
<td>66.6</td>
<td>Not specified</td>
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<tr>
<td>Siepmann et al, 2006</td>
<td>MMF</td>
<td>40.1</td>
<td>12.3</td>
<td>49</td>
<td>--</td>
<td>55.75</td>
<td>Idio</td>
<td>80.4</td>
<td>Corticosteroids +CsA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44.8</td>
<td>11</td>
<td>43.5</td>
<td>--</td>
<td>--</td>
<td>Idio</td>
<td>62.2</td>
<td>Pos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>57.3</td>
<td>8.5</td>
<td>33</td>
<td>--</td>
<td>--</td>
<td>Idio</td>
<td>50</td>
<td>Pan</td>
</tr>
<tr>
<td>Linares-Tello et al,</td>
<td>MMF</td>
<td>40</td>
<td>16.5</td>
<td>42</td>
<td>21.4</td>
<td>3.5</td>
<td>Idio</td>
<td>67</td>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>

**Legend:** Idio= Idiopathic, Pos= Posterior, Int= Intermediate, Pan= Panuveitis, Pred= Prednisone, %= Frequency of patients
Table 22: Mycophenolate Mofetil Treatment, Descriptive Outcomes

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>IMVA</th>
<th>IMI</th>
<th>Primary Discontinuation reason</th>
<th>%</th>
<th>Secondary Discontinuation reason</th>
<th>%</th>
<th>Primary Adverse events</th>
<th>%</th>
<th>Secondary Adverse events</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capriotti et al, 2005¹⁴¹</td>
<td>MMF</td>
<td>81.1</td>
<td>60.9</td>
<td>Intolerance</td>
<td>16</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Bhat et al, 2009¹⁴²</td>
<td>MMF</td>
<td>64.3</td>
<td>100</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Leukopenia</td>
<td>43</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Neri et al, 2009¹⁴³</td>
<td>MMF</td>
<td>94.7</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Dyspepsia</td>
<td>31.6</td>
<td>Tiredness</td>
<td>26.3</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Benson et al, 2006¹⁴⁴</td>
<td>MMF</td>
<td>--</td>
<td>--</td>
<td>Gastrointestinal</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Gastrointestinal</td>
<td>14.3</td>
<td>Fatigue</td>
<td>0.1</td>
</tr>
<tr>
<td>Daniel et al, 2010¹⁴⁵</td>
<td>MMF</td>
<td>--</td>
<td>73.1</td>
<td>Side Effects</td>
<td>12</td>
<td>Ineffectiveness</td>
<td>9.7</td>
<td>Gastrointestinal</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Deuter et al, 2009¹⁴⁶</td>
<td>Mycophenolate sodium</td>
<td>92.3</td>
<td>94.2</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Gastrointestinal</td>
<td>14.3</td>
<td>Fatigue</td>
<td>0.1</td>
</tr>
<tr>
<td>Doycheva et al, 2012¹⁴⁷</td>
<td>MMF</td>
<td>76.3</td>
<td>--</td>
<td>Herpes zoster dermatitis, kidney infection, and gastrointestinal</td>
<td>8.9</td>
<td>--</td>
<td>--</td>
<td>Gastrointestinal</td>
<td>14.3</td>
<td>Fatigue</td>
<td>0.1</td>
</tr>
<tr>
<td>Zierhut et al, 2011¹⁴⁸</td>
<td>MMF</td>
<td>81.7</td>
<td>72</td>
<td>Efficacy</td>
<td>35</td>
<td>Inefficacy</td>
<td>20</td>
<td>Gastrointestinal</td>
<td>23.3</td>
<td>Muscle pain</td>
<td>8.3</td>
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<tr>
<td>Stuebiger et al, 2007¹⁴⁹</td>
<td>MMF</td>
<td>76.5</td>
<td>82.3</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Headache</td>
<td>23.5</td>
<td>Rash</td>
<td>11.8</td>
</tr>
<tr>
<td>Forrester et al, 1998¹⁵⁰</td>
<td>MMF</td>
<td>86.7</td>
<td>86.7</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Myalgia</td>
<td>44.4</td>
<td>Fatigue</td>
<td>22.2</td>
</tr>
<tr>
<td>Siepmann et al, 2006¹⁵¹</td>
<td>MMF</td>
<td>100</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Gastrointestinal</td>
<td>23.3</td>
<td>Muscle pain</td>
<td>8.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td>100</td>
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<td>--</td>
<td>Headache</td>
<td>--</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>66.6</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Headache</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Llinares-Tello et al, 2004¹⁵²</td>
<td>MMF</td>
<td>83</td>
<td>--</td>
<td>Therapeutic failure</td>
<td>17</td>
<td>Diarrhoea</td>
<td>25</td>
<td>Agitation</td>
<td>25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend**: IMVA= Improving or maintaining Visual Acuity, IMI= Improving or maintaining Inflammation, % = Frequency of patients
6.2.2.2 Methotrexate

6.2.2.2.1 Study Characteristics

Of the studies that examined MTX, 7 studies were conducted in the USA, 1 study in Germany, and the other in Israel. The studies collected patient data from as early as 1986 (Friling et al\(^\text{153}\)), and the latest data was collected in Khan et al in 2008. The full paper could not be attained for 2 studies, Khan et al (2010)\(^\text{154}\) and Schmitt et al (1990)\(^\text{155}\) For these 2 studies we only had abstracts, however they contained the essential information. Seven studies were retrospective case series, whereas 1 study was a prospective randomized pilot study, and the other was randomized control trial, double-masked study. Study characteristics are summarized in Table 23.

6.2.2.2.2 Study Size and Patient Characteristics

The total sample size for the MMF studies was 691. Across the studies, the mean age of patients that were given MTX ranged from 16.7 to 49 years. Most studies had a mean age in the 40s, while 1 study that looked at juvenile idiopathic patients had a mean age of 16.7 years. In all studies, females made up the majority of the patient population (ranging from 64% to 91%). Mean reported follow up time ranged from 3.9 to 164 months, with 2 studies not reporting

All studies included patients with idiopathic uveitis, with 1 study specifically looking at juvenile idiopathic uveitis, averaging at 78% of patients having idiopathic uveitis. Uveitis type was not specified in 5 of the studies, while intermediate, posterior, and mixed were each reported in 1 study. Seven studies had prior steroid usage, 1 had steroid with immunosuppressive treatment, and 1 did not specify prior treatment. Patient characteristics are summarized in Table 24.

6.2.2.2.3 Descriptive Outcomes

One measure of effectiveness used was the frequency of patients for who VA was improved or maintained. Five studies indicated that MTX was effective in treating patients, ranging from 76% to 100% of patients experiencing maintained or improved
VA, with 4 studies not reporting. The improvement or maintaining of inflammation grade was exhibited in 2 studies. Yu et al (2005)\textsuperscript{156} indicated that the inflammation grade for 50\% of patients had improved or maintained, while Dev et al (1999)\textsuperscript{157} indicated that the inflammation grade for 95\% of patients had improved or maintained.

### 6.2.2.2.4 Reason for Discontinuation and Adverse Events

Five out of 10 studies indicated that MTX was discontinued in some patients due to lack of efficacy, with frequency ranging from 13\% to 48\% of patients. With one study having had patients discontinue treatment due to side effects. Five studies reported adverse events of MTX. Some patients experienced higher leukopenia (14\% of patients), higher anemia (14\%), mild increase in SGOT (13\%), minimal increase in creatinine (7\%), fatigue (19\%), mild nausea (19\%), and gastrointestinal issues (20\%). Descriptive outcomes, including the adverse events, are summarized in Table 25.

### Table 23: Methotrexate Treatment, Study Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Design</th>
<th>Setting/Data source</th>
<th>Accrual Period</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker et al, 2006\textsuperscript{158}</td>
<td>Methotrexate</td>
<td>Retrospective case series</td>
<td>Casey Eye Institute (Portland, Oregon, USA)</td>
<td>2003</td>
<td>107</td>
</tr>
<tr>
<td>Foeldvari et al, 2004\textsuperscript{159}</td>
<td>Methotrexate</td>
<td>Retrospective case series</td>
<td>Germany</td>
<td>July 1, 2002 to December 31, 2002</td>
<td>467</td>
</tr>
<tr>
<td>Friling et al, 2005\textsuperscript{153}</td>
<td>Methotrexate</td>
<td>Retrospective Case Series</td>
<td>Israel</td>
<td>38 consecutive children between 1986 to 2002</td>
<td>15</td>
</tr>
<tr>
<td>Khan et al*, 2010\textsuperscript{154}</td>
<td>Methotrexate</td>
<td>Retrospective Case Series</td>
<td>USA</td>
<td>1997 to 2008</td>
<td>36</td>
</tr>
<tr>
<td>Quinones et al, 2010\textsuperscript{160}</td>
<td>Methotrexate</td>
<td>Prospective Randomized Pilot Study</td>
<td>USA</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Schmitt et al*, 1990\textsuperscript{155}</td>
<td>Methotrexate</td>
<td>Retrospective Case Series</td>
<td>USA</td>
<td>--</td>
<td>15</td>
</tr>
<tr>
<td>Yu et al, 2005\textsuperscript{156}</td>
<td>Methotrexate</td>
<td>Retrospective Case Series</td>
<td>Massachusetts Eye and Ear Infirmary, USA</td>
<td>1981 and 2001</td>
<td>23</td>
</tr>
<tr>
<td>Dev et al, 1999\textsuperscript{157}</td>
<td>Methotrexate</td>
<td>Retrospective non-comparative case series</td>
<td>USA</td>
<td>1989 to 1997</td>
<td>11</td>
</tr>
<tr>
<td>Foster et al, 2003\textsuperscript{161}</td>
<td>Methotrexate +Placebo</td>
<td>Randomized control trial, Double masked</td>
<td>USA</td>
<td>--</td>
<td>10</td>
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</tbody>
</table>

*abstract
<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Mean Age</th>
<th>Age SD</th>
<th>%Female</th>
<th>Mean Follow-up (Mo.)</th>
<th>Mean Follow-up SD</th>
<th>Prim. Cause</th>
<th>%</th>
<th>Location of Disease</th>
<th>%</th>
<th>Previous Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker et al, 2006&lt;sup&gt;158&lt;/sup&gt;</td>
<td>MTX</td>
<td>49</td>
<td>17.6</td>
<td>70</td>
<td>164.3</td>
<td>--</td>
<td>Idio</td>
<td>58</td>
<td>--</td>
<td>--</td>
<td>Corticosteroids + immunomodulatory</td>
</tr>
<tr>
<td>Foeldvari et al, 2004&lt;sup&gt;159&lt;/sup&gt;</td>
<td>MTX</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>JIA</td>
<td>100</td>
<td>--</td>
<td>--</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Friling et al, 2005&lt;sup&gt;153&lt;/sup&gt;</td>
<td>MTX</td>
<td>--</td>
<td>--</td>
<td>67</td>
<td>3.9</td>
<td>2.8</td>
<td>Idio</td>
<td>100</td>
<td>--</td>
<td>--</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Khan et al*, 2010&lt;sup&gt;154&lt;/sup&gt;</td>
<td>MTX</td>
<td>43.5</td>
<td>14.25</td>
<td>64</td>
<td>--</td>
<td>--</td>
<td>Idio</td>
<td>53</td>
<td>Posterior, intermediate and panuveitis</td>
<td>100</td>
<td>--</td>
</tr>
<tr>
<td>Quinones et al, 2010&lt;sup&gt;160&lt;/sup&gt;</td>
<td>MTX</td>
<td>34.54</td>
<td>11.75</td>
<td>57</td>
<td>5.44</td>
<td>1.2</td>
<td>Idio</td>
<td>85.7</td>
<td>Intermediate</td>
<td>100</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Schmitt et al*, 1990&lt;sup&gt;155&lt;/sup&gt;</td>
<td>MTX</td>
<td>47</td>
<td>12</td>
<td>80</td>
<td>9</td>
<td>5.5</td>
<td>idio</td>
<td>53.3</td>
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</tr>
<tr>
<td>Yu et al, 2005&lt;sup&gt;156&lt;/sup&gt;</td>
<td>MTX</td>
<td>16.7</td>
<td>10</td>
<td>91</td>
<td>7.3</td>
<td>2</td>
<td>JIA</td>
<td>100</td>
<td>--</td>
<td>--</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Dev et al, 1999&lt;sup&gt;157&lt;/sup&gt;</td>
<td>MTX</td>
<td>38</td>
<td>11.5</td>
<td>81.8</td>
<td>&lt;12 months</td>
<td>--</td>
<td>Panuveitis</td>
<td>--</td>
<td>Posterior</td>
<td>--</td>
<td>Corticosteroids (were resistant)</td>
</tr>
<tr>
<td>Foster et al, 2003&lt;sup&gt;161&lt;/sup&gt;</td>
<td>Methotrexate + Placebo</td>
<td>45</td>
<td>--</td>
<td>90</td>
<td>--</td>
<td>--</td>
<td>Idio</td>
<td>70</td>
<td>--</td>
<td>--</td>
<td>Methotrexate</td>
</tr>
</tbody>
</table>

**Legend:** Idio= Idiopathic, JIA= Juvenile idiopathic arthritis, Pos= Posterior, Int= Intermediate, Pan= Panuveitis, Pred= Prednisone, *abstract
Table 25: Methotrexate Treatment, Descriptive Outcomes

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>IMVA</th>
<th>IMI</th>
<th>Prim. Reason for discon.</th>
<th>%</th>
<th>Sec. reason for discon.</th>
<th>%</th>
<th>Primary Adverse events</th>
<th>%</th>
<th>Secondary Adverse events</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker et al, 2006</td>
<td>MTX</td>
<td>--</td>
<td>--</td>
<td>Lack of efficacy</td>
<td>36</td>
<td>Adverse events</td>
<td>26</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Foeldvari et al, 2004</td>
<td>MTX</td>
<td>76</td>
<td>--</td>
<td>Lack of efficacy</td>
<td>16</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
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</tr>
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<td>Friling et al, 2005</td>
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<td>87</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
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<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Khan et al*, 2010</td>
<td>MTX</td>
<td>--</td>
<td>--</td>
<td>--</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Quinones et al, 2010</td>
<td>MTX</td>
<td>--</td>
<td>--</td>
<td>Lack of efficacy</td>
<td>44</td>
<td>--</td>
<td>--</td>
<td>Higher leukopenia</td>
<td>14</td>
<td>Higher anemia</td>
<td>14</td>
</tr>
<tr>
<td>Schmitt et al*, 1990</td>
<td>MTX</td>
<td>--</td>
<td>--</td>
<td>Lack of efficacy</td>
<td>13</td>
<td>--</td>
<td>--</td>
<td>Mild increase in SGOT (2)</td>
<td>13</td>
<td>A minimal increase in creatinine (1)</td>
<td>7</td>
</tr>
<tr>
<td>Yu et al, 2005</td>
<td>MTX</td>
<td>86</td>
<td>50</td>
<td>Lack of efficacy</td>
<td>48</td>
<td>--</td>
<td>--</td>
<td>Fatigue</td>
<td>19</td>
<td>Mild nausea</td>
<td>19</td>
</tr>
<tr>
<td>Dev et al, 1999</td>
<td>MTX</td>
<td>90</td>
<td>95</td>
<td>Side effects</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Nausea</td>
<td>14</td>
<td>Cytopenia</td>
<td>--</td>
</tr>
<tr>
<td>Foster et al, 2003</td>
<td>Methotrexate +Placebo</td>
<td>100</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Gastrointestinal</td>
<td>0.2</td>
<td>--</td>
<td>--</td>
<td>--</td>
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</tr>
</tbody>
</table>

Legend: IMVA= Improving or maintaining Visual Acuity, IMI= Improving or maintaining Inflammation, Prim Reason= Primary, Sec= Secondary, %= Frequency of patients, MTX= Methotrexate, discon= discontinuation *abstract
6.2.2.3 Azathioprine

6.2.2.3.1 Study Characteristics

Two studies used solely AZA, and both studies were conducted in the USA, between 1977 and 2008. One study was a case series, while the other was a retrospective cohort study. Study characteristics are summarized in Table 26.

6.2.2.3.2 Study Size and Patient Characteristics

The total combined number of patients in both studies was 153. Across the studies, the mean age of patients that were given AZA ranged from 12.6 years to 50.6 years. 88% of the patients were female in the study with the juvenile patients, while 67.9% of patients were female in the second study. Reported mean follow-up time ranged from 7.67 months to 84 months. Uveitis type was only classified in 1 study as mixed, while the other did not specify. One study had prior steroid usage, while the other had steroid with immunosuppressive treatment. Patient characteristics are summarized in Table 27.

6.2.2.3.3 Descriptive Outcomes

Only 1 of the studies reported on the frequency of patients for who VA was improved or maintained, which was about 83.3%. The other study was the only one that reported on inflammation grade, for which about 62.2% of patients had improved or maintained.

6.2.2.3.4 Reason for Discontinuation and Adverse Events

Pasadihika et al (2009)\textsuperscript{162} indicated that 24% of patients given AZA discontinued treatment due to side effects, while 15% of patients discontinued treatment due to lack of efficacy. Descriptive outcomes, including the adverse events, are summarized in Table 28.
Table 26: Azathioprine Treatment, Study Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Design</th>
<th>Setting/Data source</th>
<th>Accrual Period</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasadhika et al, 2009</td>
<td>Azathioprine</td>
<td>Retrospective cohort study</td>
<td>USA</td>
<td>2005 to 2008</td>
<td>145</td>
</tr>
</tbody>
</table>
### Table 27: Azathioprine Treatment, Patient Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Mean Age</th>
<th>Age SD</th>
<th>%Female</th>
<th>Mean Follow-up (Mo.)</th>
<th>Mean Follow-up SD</th>
<th>Prim. Cause</th>
<th>%</th>
<th>Location of disease</th>
<th>%</th>
<th>Previous Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemady et al, 1992¹⁶³</td>
<td>Aza</td>
<td>12.6</td>
<td>5.2</td>
<td>88</td>
<td>84</td>
<td>28</td>
<td>JIA</td>
<td>100</td>
<td>--</td>
<td>--</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Pasadhika et al, 2009¹⁶²</td>
<td>Aza</td>
<td>50.6</td>
<td>19.2</td>
<td>67.6</td>
<td>7.67</td>
<td>5.2</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Posterior/Panuveitis /Intermediate</td>
</tr>
</tbody>
</table>

**Legend:** Prim. = Primary, % = Frequency of patients, JIA= Juvenile idiopathic arthritis

### Table 28: Azathioprine Treatment, Descriptive Outcomes

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>IMVA</th>
<th>IMI</th>
<th>Primary reason for discon.</th>
<th>%</th>
<th>Secondary reason for discon.</th>
<th>%</th>
<th>Primary Adverse events</th>
<th>%</th>
<th>Secondary Adverse events</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemady et al, 1992¹⁶³</td>
<td>Azathioprine</td>
<td>83.333</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Gastrointestinal</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Pasadhika et al, 2009¹⁶²</td>
<td>Azathioprine</td>
<td>62.2 (50.5 to 74.0)</td>
<td>Side Effects</td>
<td>24</td>
<td>Ineffectiveness</td>
<td>15</td>
<td>Gastrointestinal</td>
<td>9</td>
<td>Bone marrow suppression</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

**Legend:** IMVA= Improving or maintaining Visual Acuity, IMI= Improving or maintaining Inflammation, % = Frequency of patients, discon= discontinuation
6.2.3 Alkylating Agents

6.2.3.1 Chlorambucil

6.2.3.1.1 Study Characteristics

One study explored the use of Chlorambucil. It was a non-comparative interventional case series conducted in the USA, between 1987 and 2000. Study characteristics are summarized in Table 29.

6.2.3.1.2 Study Size and Patient Characteristics

There were 28 patients in the study, with a mean age of 28.8 years, and 92.8% female patients. The mean follow-up was 46 months. Juvenile rheumatoid arthritis patients with idiopathic uveitis accounted for 66% of the patients. Location of the disease in all patients was panuveitis. Patients had previously been treated with steroids, CsA, AZA, and/or MTX. Patient characteristics are summarized in Table 30.

6.2.3.1.3 Descriptive Outcomes

VA was maintained or improved in 82.1% of patients, and the inflammation grade maintained or improved in 67.9% of the patients.

6.2.3.1.4 Reason for Discontinuation and Adverse Events

Gastrointestinal intolerance and leukopenia accounted for AZA treatment being discontinued in 14.2% of patients. Descriptive outcomes, including adverse events, are summarized in Table 31.

Table 29: Chlorambucil Treatment, Study Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Design</th>
<th>Setting/Data source</th>
<th>Accrual Period</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miserocchi et al, 2002</td>
<td>Chlorambucil</td>
<td>Non-comparative interventional case series</td>
<td>Ocular Immunology and Uveitis Service of the Massachusetts Eye and Ear Infirmary</td>
<td>1987 to 2000</td>
<td>28</td>
</tr>
</tbody>
</table>
### Table 30: Chlorambucil Treatment, Patient Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Age (SD)</th>
<th>Age (SD)</th>
<th>%Female</th>
<th>Mean Follow-up (Mo.)</th>
<th>Mean Follow-up SD</th>
<th>Primary Cause</th>
<th>%</th>
<th>Location of Disease</th>
<th>%</th>
<th>Previous Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miserocchi et al, 2002</td>
<td>Chlorambucil</td>
<td>28.75 (16.3)</td>
<td>92.8</td>
<td>46</td>
<td>40.5</td>
<td></td>
<td>Juvenile rheumatoid arthritis–associated uveitis</td>
<td>55.7</td>
<td>Posterior/ Panuveitis/ Intermediate</td>
<td>60.7</td>
<td>Pred, CsA, AZA, MTX</td>
</tr>
</tbody>
</table>

### Table 31: Chlorambucil Treatment, Descriptive Outcomes

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>IMVA</th>
<th>IMI</th>
<th>Reason for discontinuation</th>
<th>Primary reason for discon.</th>
<th>%</th>
<th>Secondary reason for discon.</th>
<th>%</th>
<th>Primary Adverse events</th>
<th>%</th>
<th>Secondary Adverse events</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miserocchi et al, 2002</td>
<td>Chlorambucil</td>
<td>82.1</td>
<td>67.9</td>
<td>Side effects</td>
<td>Gastrointestinal intolerance</td>
<td>7.1</td>
<td>Leukopenia</td>
<td>7.1</td>
<td>Gastrointestinal</td>
<td>7.1</td>
<td>Leukopenia</td>
<td>7.1</td>
</tr>
</tbody>
</table>

**Legend:** IMVA = Improving or maintaining Visual Acuity, IMI = Improving or maintaining Inflammation, % = Frequency of patients, discon = discontinuation
6.2.4 Studies with Multiple Treatments

The majority of patients in the studies were idiopathic uveitis patients, with 3 studies having 100% of the patients being idiopathic in nature. Two studies included individual patients who were administered multiple treatments in the same study. The first, BenEzra (1990)\(^{165}\), was a retrospective case series conducted in Israel between 1979 and 1987. Three treatments were prescribed to patients: Chlorambucil (n=46), AZA (n=23), and CsA (n=24). The treatment administered to patients prior to Chlorambucil and AZA was corticosteroids; patients were given corticosteroids with AZA or Chlorambucil before they were given CsA. VA was maintained or improved in 83% of patients treated with Chlorambucil, in 50% of patients treated with AZA, and in 90% of patients treated with CsA. Inflammation grade was maintained or improved in 83% of patients treated with Chlorambucil. The study did not report any improvement to inflammation grade for patients treated with AZA and CsA. Lack of efficacy led to treatment discontinuation in 23% of Chlorambucil-treated patients.

The second study, Dick et al (1997)\(^{166}\), was a retrospective case series conducted in Scotland between 1992 and 1996. The first group contained 54 posterior uveitis patients with a mean age of 44.6 years. They were administered steroids and CsA. The second group contained 24 posterior uveitis patients with a mean age of 46.2 years. They were administered steroids, CsA and AZA. There were no outcomes reported, however, measurements of pre-treatment and post-treatment VA were reported in the meta-analysis. Study and patient characteristics for multiple treatments are summarized in Tables 32 and 33, respectively, and descriptive outcomes, including adverse events, are summarized in Table 34.
### Table 32: Multiple Treatments, Patient Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Design</th>
<th>Setting/Data source</th>
<th>Accrual Period</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>BenEzra, 1990</td>
<td>Chlorambucil</td>
<td>Retrospective Case series</td>
<td>Israel</td>
<td>1979-1987 (patients followed for 2 years)</td>
<td>46</td>
</tr>
<tr>
<td>AZA</td>
<td>Retropective Case series</td>
<td>Israel</td>
<td>1979-1987 (patients followed for 2 years)</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>CsA</td>
<td>Retropective Case series</td>
<td>Israel</td>
<td>1979-1987 (patients followed for 2 years)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Dick et al, 1997</td>
<td>Prednisone + Cyclosporine A</td>
<td>Retrospective Case series</td>
<td>Scotland, Europe</td>
<td>1992 to 1996</td>
<td>54</td>
</tr>
<tr>
<td>Prednisone + Cyclosporine A + AZA</td>
<td>Retrospective Case series</td>
<td>Scotland, Europe</td>
<td>1992 to 1996</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

**Legend:** AZA= Azathioprine, CsA= Cyclosporine
Table 33: Multiple Treatments, Patient Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Mean Age</th>
<th>Age SD</th>
<th>%Female</th>
<th>Mean Follow-up (Mo.)</th>
<th>Mean Follow-up SD</th>
<th>Primary Cause</th>
<th>%</th>
<th>Location of disease</th>
<th>%</th>
<th>Previous Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BenEzra, 1990165</td>
<td>Chlorambucil</td>
<td>--</td>
<td>--</td>
<td>34</td>
<td>8</td>
<td>4</td>
<td>Idiopathic</td>
<td>67</td>
<td>--</td>
<td>--</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine A</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Dick et al, 1997166</td>
<td>Prednisone + Cyclosporine A</td>
<td>54</td>
<td>13.6</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Idiopathic</td>
<td>100</td>
<td>Posterior</td>
<td>--</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Prednisone + Cyclosporine A + Azathioprine</td>
<td>24</td>
<td>19.9</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Idiopathic</td>
<td>100</td>
<td>Posterior</td>
<td>--</td>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>

Table 34: Multiple Treatments, Descriptive Outcomes

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Improved or maintained VA # 1</th>
<th>Controlling intraocular inflammation # 1</th>
<th>Primary reason for discon.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>BenEzra, 1990165</td>
<td>Chlorambucil</td>
<td>83</td>
<td>83</td>
<td>Lack of efficacy</td>
<td>23</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>50</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>92</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Dick et al, 1997166</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Legend: Discon= Discontinuation
6.2.5 Studies With No Specification Regarding Which Immunosuppressive Was Used

Three studies only mentioned that immunosuppressives were used as treatment, without specifying the exact treatment group. Two studies were a retrospective case series, 1 was a retrospective cohort study. Two studies were conducted in the USA between 1978 and 2005. The total sample size across the 3 studies was 174. Two studies included the ages of the patients; 1 was conducted with JIA patients, so the mean age was 9 years, with a range of 1 to 17 years. The other was conducted with panuveitis uveitis patients, where the mean age was 45 years, with a range of 9 years to 80 years. Gender proportions ranged from 75.8-82% female. Only 1 study specified the uveitis location classification as panuveitis. Corticosteroids were used as prior treatment in all 3 studies. One study reported that VA was maintained or improved for 100% of patients. None of the studies reported on treatment discontinuation or adverse events. Study and patient characteristics for non-specific immunosuppressive treatments are summarized in Tables 35 and 36, respectively, and descriptive outcomes are summarized in Table 37.

Table 35: Immunomodulators, Study Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Design</th>
<th>Setting/Data source</th>
<th>Accrual Period</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michel et al, 2002167</td>
<td>Immunomodulators</td>
<td>Retrospective, non-comparative, interventional case series</td>
<td>USA</td>
<td>1978 to 2000</td>
<td>19</td>
</tr>
<tr>
<td>Kump et al, 2006169</td>
<td>Immunomodulators</td>
<td>Retrospective Case Series</td>
<td>USA</td>
<td>1985 through 2003</td>
<td>89</td>
</tr>
<tr>
<td>Throne et al, 2006168</td>
<td>Immunosuppressive drug therapy</td>
<td>Retrospective Cohort Study</td>
<td>Ocular Immunology at the Wilmer Eye Institute</td>
<td>January 1984 and June 2005</td>
<td>66</td>
</tr>
</tbody>
</table>
Table 36: Immunomodulators, Patient Characteristics

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Age</th>
<th>Age SD</th>
<th>%Female</th>
<th>Mean Follow-up (Mo.)</th>
<th>Mean Follow-up SD</th>
<th>Primary Cause</th>
<th>%</th>
<th>Location of disease</th>
<th>%</th>
<th>Previous Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michel et al, 2002¹⁶⁷</td>
<td>Immunomodulators</td>
<td>9</td>
<td>4.5</td>
<td>82</td>
<td>35.52</td>
<td>--</td>
<td>Juvenile idiopathic arthritis</td>
<td>53</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Kump et al, 2006¹⁶⁸</td>
<td>Immunosuppressive drug therapy</td>
<td>45</td>
<td>17.8</td>
<td>75.8</td>
<td>--</td>
<td>--</td>
<td>Panuveitis</td>
<td>100</td>
<td>Panuveitis</td>
<td>100</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Throne et al, 2006¹⁶⁹</td>
<td>Immunomodulators</td>
<td>--</td>
<td>--</td>
<td>78.9</td>
<td>72.7</td>
<td>55.8</td>
<td>Panuveitis</td>
<td>100</td>
<td>--</td>
<td>--</td>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>

Table 37: Immunomodulators, Descriptive Outcomes

<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Improved or maintained VA # 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michel et al, 2002¹⁶⁷</td>
<td>Immunomodulators</td>
<td>--</td>
</tr>
<tr>
<td>Kump et al, 2006¹⁶⁸</td>
<td>Immunosuppressive drug therapy</td>
<td>--</td>
</tr>
<tr>
<td>Throne et al, 2006¹⁶⁹</td>
<td>Immunomodulators</td>
<td>100</td>
</tr>
</tbody>
</table>
6.3 Risk of Bias within Studies

The quality of the studies included in this systematic review was analyzed using a modified Downs and Black checklist. Of the 45 studies we looked at, only 41 were included in the assessment; the 4 excluded studies were abstracts.

6.3.1 Randomized Controlled Trials

When we applied the modified Downs and Black checklist, the median score for the quality of the 5 RCT studies was 60%, with an interquartile range of 7%. The risk of bias in the RCTs is presented in Figure 4 on the following page.

The RCT studies included additional questions specifically about randomization and blinding of patients.

Only 2 of the 5 RCT studies did all of the following: randomized and blinded patients to the treatment, listed confounders, blinded those measuring the main outcome, and randomized intervention assignment that was concealed from the patients and staff until the recruitment was complete.

Three studies had adequate adjustment for confounding in analysis; losses of patients to follow-up were not taken into account, and no power calculation was done. Of the 10 reporting bias questions, 7 questions were answered yes in all 5 studies. The 3 questions pertaining to external validity were answered yes in all studies. Of the 7 internal validity bias questions, 1 question was answered yes for all studies, while 2 other questions were answered yes for only 3 studies. As for selection bias, only 1 of the 6 questions had a yes from all studies, and was poorly rated in the studies overall.

6.3.2 Observational Studies

After using the checklist on the 37 observational studies, the median score for the quality of the studies was 48%, with an interquartile range of 5%. The risk of bias in the observational studies is presented in Figure 4.
Three questions from the internal validity section were removed, and 2 questions from the selection bias section were removed, as they pertained mainly to randomized trials. The principal confounders were clearly described in 10% of studies. Patients that were lost to follow-up were described in 12.5% of studies. 15% of studies listed the probability values for the main outcomes, 5% indicated follow-up of patients was the same for all study participants, and 17.5% used appropriate statistical tests to assess the main outcomes.

Of the 10 reporting bias questions, 7 questions were answered yes in >80% of studies. The 3 questions pertaining to external validity were answered with yes in >80% of studies. Of the 4 internal validity bias questions, 1 question was answered yes in >80% of studies. As for selection bias, only 1 of the 4 questions had a yes in 87.5% of studies.

![Figure 4: Risk of Bias and Internal/External Validity](image-url)
6.4 Meta-analysis

6.4.1 Results of Individual Studies

Majority of the patients were idiopathic uveitis patients, with posterior or intermediate uveitis, this can be seen with the data from the systematic review. As discussed in section 5.5, VA was used as the primary outcome to measure efficacy. VA was measured using logMAR in some studies, while in other studies VA was converted to logMAR from other scales. Inflammation grade change was not reported among enough studies having a standardized scale for inflammation grade to allow for any meaningful conclusions. Table 38 indicates the results from the 26 individual studies.

For our study, we had independent subgroups within a study, which allowed them to be viewed as independent studies. Because of this, the count of studies went from 26 to 32. However, 6 studies had some missing data, either with pre- and post-logMAR, or pre- and post-logMAR standard deviation, thus it was extrapolated, and these studies are noted in bold print in Table 38.
Table 38: Results of Individual Studies: pre- and post-logMAR

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Prim Treatment</th>
<th>Prev</th>
<th>Age (year)</th>
<th>Loc</th>
<th>Pre-logMAR</th>
<th>Pre-SD</th>
<th>Post-logMAR</th>
<th>Post-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friling et al</td>
<td>2005</td>
<td>15</td>
<td>MTX</td>
<td>Steros</td>
<td>10.5</td>
<td>Int</td>
<td>0.357</td>
<td>2.18</td>
<td>0.052</td>
<td>0.103</td>
</tr>
<tr>
<td>Lee Richard et al</td>
<td>2012</td>
<td>19</td>
<td>Steroid + Tac</td>
<td>Steros</td>
<td>32.3</td>
<td>Pos</td>
<td>0.57</td>
<td>2.18</td>
<td>0.561</td>
<td>2.42</td>
</tr>
<tr>
<td>Lee Richard et al</td>
<td>2012</td>
<td>16</td>
<td>Tac</td>
<td>Steros</td>
<td>41.8</td>
<td>Pos</td>
<td>0.57</td>
<td>2.18</td>
<td>0.579</td>
<td>2.245</td>
</tr>
<tr>
<td>Murphy et al</td>
<td>2005</td>
<td>19</td>
<td>Tac</td>
<td>Steros</td>
<td>49</td>
<td>Pan</td>
<td>0.335</td>
<td>0.225</td>
<td>0.248</td>
<td>0.304</td>
</tr>
<tr>
<td>Murphy et al</td>
<td>2005</td>
<td>18</td>
<td>CsA</td>
<td>Steros</td>
<td>38</td>
<td>Pan</td>
<td>0.45</td>
<td>0.289</td>
<td>0.326</td>
<td>0.302</td>
</tr>
<tr>
<td>Quinones et al</td>
<td>2010</td>
<td>7</td>
<td>MTX</td>
<td>Steros</td>
<td>34.5</td>
<td>Int</td>
<td>0.57</td>
<td>2.18</td>
<td>0.514</td>
<td>2.292</td>
</tr>
<tr>
<td>Rosales et al</td>
<td>2011</td>
<td>75</td>
<td>CsA</td>
<td>Steros</td>
<td>42</td>
<td>NS</td>
<td>0.57</td>
<td>2.18</td>
<td>0.47</td>
<td>2.61</td>
</tr>
<tr>
<td>Walton et al</td>
<td>1998</td>
<td>15</td>
<td>CsA</td>
<td>NS</td>
<td>12.9</td>
<td>Int</td>
<td>0.176</td>
<td>0.265</td>
<td>0.218</td>
<td>0.262</td>
</tr>
<tr>
<td>Yu et al</td>
<td>2005</td>
<td>23</td>
<td>MTX</td>
<td>Steros</td>
<td>16.7</td>
<td>NS</td>
<td>0.968</td>
<td>0.824</td>
<td>0.803</td>
<td>0.974</td>
</tr>
<tr>
<td>Bhat et al</td>
<td>2009</td>
<td>7</td>
<td>MMF</td>
<td>Imm</td>
<td>49</td>
<td>Pan</td>
<td>0.52</td>
<td>0.72</td>
<td>0.43</td>
<td>0.77</td>
</tr>
<tr>
<td>Dev et al</td>
<td>1999</td>
<td>11</td>
<td>MTX</td>
<td>Steros</td>
<td>38</td>
<td>Pos</td>
<td>0.415</td>
<td>0.491</td>
<td>0.23</td>
<td>0.361</td>
</tr>
<tr>
<td>Kump et al</td>
<td>2006</td>
<td>89</td>
<td>Comb</td>
<td>NS</td>
<td>5.7</td>
<td>NS</td>
<td>0.471</td>
<td>0.42</td>
<td>0.403</td>
<td>0.393</td>
</tr>
<tr>
<td>Rocha et al</td>
<td>1997</td>
<td>8</td>
<td>CsA</td>
<td>Imm</td>
<td>39</td>
<td>Pan</td>
<td>1.19</td>
<td>0.97</td>
<td>1.04</td>
<td>1.02</td>
</tr>
<tr>
<td>Neri et al</td>
<td>2009</td>
<td>19</td>
<td>MMF</td>
<td>Imm</td>
<td>32.9</td>
<td>Int</td>
<td>0.34</td>
<td>0.14</td>
<td>0.67</td>
<td>0.18</td>
</tr>
<tr>
<td>Deuter et al</td>
<td>2009</td>
<td>35</td>
<td>MMF</td>
<td>Steros</td>
<td>42.7</td>
<td>Comb</td>
<td>0.38</td>
<td>0.47</td>
<td>0.38</td>
<td>0.51</td>
</tr>
<tr>
<td>Figueroa et al</td>
<td>2007</td>
<td>11</td>
<td>Tac</td>
<td>Imm</td>
<td>40.6</td>
<td>Pos</td>
<td>0.868</td>
<td>0.623</td>
<td>0.913</td>
<td>0.652</td>
</tr>
<tr>
<td>Hogan et al</td>
<td>2007</td>
<td>62</td>
<td>Tac</td>
<td>Imm</td>
<td>38</td>
<td>Pos</td>
<td>0.297</td>
<td>0.322</td>
<td>0.233</td>
<td>0.319</td>
</tr>
<tr>
<td>Kilmartin et al</td>
<td>1925</td>
<td>14</td>
<td>CsA</td>
<td>Steros</td>
<td>8.7</td>
<td>Int</td>
<td>0.5688</td>
<td>0.561</td>
<td>0.405</td>
<td>0.539</td>
</tr>
<tr>
<td>Miserochhi et al</td>
<td>2002</td>
<td>28</td>
<td>Chlorambucil</td>
<td>Imm</td>
<td>28.8</td>
<td>Comb</td>
<td>0.776</td>
<td>0.761</td>
<td>0.63</td>
<td>0.844</td>
</tr>
<tr>
<td>Siepmann et al</td>
<td>2006</td>
<td>51</td>
<td>MMF</td>
<td>NS</td>
<td>40.1</td>
<td>Int</td>
<td>0.458</td>
<td>0.33</td>
<td>0.293</td>
<td>0.299</td>
</tr>
<tr>
<td>Siepmann et al</td>
<td>2006</td>
<td>23</td>
<td>MMF</td>
<td>NS</td>
<td>44.8</td>
<td>Pos</td>
<td>0.545</td>
<td>0.352</td>
<td>0.465</td>
<td>0.39</td>
</tr>
<tr>
<td>Siepmann et al</td>
<td>2006</td>
<td>6</td>
<td>MMF</td>
<td>NS</td>
<td>57.3</td>
<td>Pan</td>
<td>0.613</td>
<td>0.273</td>
<td>0.546</td>
<td>0.368</td>
</tr>
<tr>
<td>Doycheva et al</td>
<td>2012</td>
<td>38</td>
<td>MMF</td>
<td>Steros</td>
<td>42.4</td>
<td>Int</td>
<td>0.564</td>
<td>0.509</td>
<td>0.427</td>
<td>0.547</td>
</tr>
<tr>
<td>Hemady et al</td>
<td>1992</td>
<td>8</td>
<td>Aza</td>
<td>Steros</td>
<td>12.6</td>
<td>NS</td>
<td>0.834</td>
<td>0.664</td>
<td>0.551</td>
<td>0.527</td>
</tr>
<tr>
<td>Dick et al</td>
<td>1997</td>
<td>54</td>
<td>Steroids + CsA</td>
<td>Steros</td>
<td>45.6</td>
<td>Pos</td>
<td>0.593</td>
<td>0.68</td>
<td>0.549</td>
<td>0.654</td>
</tr>
<tr>
<td>Dick et al</td>
<td>1997</td>
<td>24</td>
<td>Steroids + CsA + Aza</td>
<td>Steros</td>
<td>47.2</td>
<td>Pos</td>
<td>0.489</td>
<td>0.624</td>
<td>0.615</td>
<td>0.683</td>
</tr>
<tr>
<td>Ramadan et al</td>
<td>1996</td>
<td>6</td>
<td>CsA</td>
<td>Steros</td>
<td>35.7</td>
<td>Pos</td>
<td>0.57</td>
<td>2.18</td>
<td>0.67</td>
<td>2.306</td>
</tr>
<tr>
<td>Ramadan et al</td>
<td>1996</td>
<td>6</td>
<td>CsA + Ketoconazole</td>
<td>Imm</td>
<td>35.7</td>
<td>Pos</td>
<td>0.57</td>
<td>2.18</td>
<td>0.697</td>
<td>2.21</td>
</tr>
<tr>
<td>Forrester et al</td>
<td>1998</td>
<td>9</td>
<td>MMF</td>
<td>Imm</td>
<td>39.5</td>
<td>NS</td>
<td>0.584</td>
<td>2.18</td>
<td>0.452</td>
<td>1.02</td>
</tr>
<tr>
<td>Nussenblatt et al</td>
<td>1985</td>
<td>52</td>
<td>CsA</td>
<td>Imm</td>
<td>35</td>
<td>Int</td>
<td>0.824</td>
<td>0.47</td>
<td>0.571</td>
<td>0.455</td>
</tr>
<tr>
<td>Stuebiger et al</td>
<td>2007</td>
<td>17</td>
<td>MMF</td>
<td>Steros</td>
<td>8</td>
<td>Int</td>
<td>0.57</td>
<td>2.18</td>
<td>0.464</td>
<td>2.45</td>
</tr>
<tr>
<td>Rubin et al</td>
<td>1993</td>
<td>32</td>
<td>CsA</td>
<td>Steros</td>
<td>33.8</td>
<td>Comb</td>
<td>0.877</td>
<td>0.496</td>
<td>0.52</td>
<td>0.422</td>
</tr>
</tbody>
</table>

*Pre- and post-logMAR and logMAR SD were used to calculate change in logMAR, and the change in SD in Stata and excel. The bolded studies were missing either logMAR SD (n=1) or pre-/post-logMAR (n=5); the highest SD for the missing SD and mean pre-/post-logMAR was used for missing pre/post data.

**Legend:** Prim= Primary, Prev= Previous treatment, Loc= Location of disease, pre or post-logMAR= logMAR before or after primary treatment, SD= Standard deviation, MTX= Methotrexate, TAC= Tacrolimus, CsA= Cyclosporine, MMF= Mycophenolate Mofetil, Comb= Combination of treatments given at the same time/or patients with different locations, AZA= Azathioprine, Imm= Immunomodulatory, NS= not specified, int= Intermediate uveitis, pos= positive uveitis, pan= panuveitis.
6.4.2 Primary Analysis

The summary of the results from the pooled meta-analysis and the subgroup analysis is shown in Table 39. Figure 5 below displays the forest plots of random effects pooled meta-analysis of the weighted mean difference in logMAR, where a negative change in logMAR is improvement in vision and positive change in logMAR is deteriorated vision. The studies with an asterisk (*) on them, are studies that have independent subgroups within the study. From the forest plot, it is also important to note that I+V means fixed effect model, whereas D+L means random effects model, and IMM means immunosuppressive treatments.

Since 6 studies had missing pre- and post-SD data, we imputed SD by using the highest SD reported among the overall results. The total sample size was 817 patients across all 32 analyzed studies. In the pooled random effects analyses, the immunosuppressive treatment was significantly associated with a decrease in change in logMAR (WMD -0.107 with 95% CI of -0.152 to -0.061, p= 0) and the I^2 was 0%, p=0.987. Of note, 25 studies (78.3%) reported that immunosuppressive treatment reduced logMAR.

6.4.3 Sensitivity Analysis

Out of the 26 studies, 6 had extrapolated data, so they were removed to conduct a sensitivity analysis. From the overall total of 32 studies, 8 studies were removed because they did not have the pre-/post-VA or SD, leaving only 24 studies in the sensitivity analysis. The adjusted WMD was similar to the WMD from the original pooled data that included the 8 studies (WMD -0.107 with 95% CI of -0.155 to -0.062, p=0). The I^2 of the sensitivity analysis was 0% as well. This can be seen in Figure 6 below.

6.4.4 Subgroup Analysis

6.4.4.1 Subgroup Analysis by Age

Ten studies included patients with a mean age younger than 18 years. Twenty-two studies included patients that were older than or equal to 18 years old. For patients older than or equal to 18 years old, immunosuppressive treatment had a positive statistically significant
impact on logMAR, with vision improving by -0.147 logMAR (WMD -0.147, 95% CI -0.208 to -0.097, p=0, I²=0%, p=0.990). For patients younger than 18 years, there was a slight increase in logMAR, but it was not significant (WMD -0.052, 95% CI -0.122 to 0.015, p=0.128 and I²=76.5% p=0.954). This can been seen in Figure 7.

6.4.4.2 Subgroup Analysis by Location

Nine studies containing intermediate uveitis patients indicated that patients had improved vision, with a WMD of -0.146 logMAR, which was statistically significant (95% CI -0.226 to -0.0666, p=0, I²=0%, p=0.677). Ten studies containing posterior uveitis patients had a WMD of -0.069, which was not significant (95% confidence interval -0.15 to 0.01 p=0.191, I²=0% p=0.996). Five studies containing patients with panuveitis had a WMD of -0.10, p=0.098 (95% CI - 0.22 to 0.018, I²=0%). Three studies included a combination of all 3 locations, and the patients that had uveitis in 1 of the 3 locations experienced improved vision, with a WMD of -0.172 and a p-value of 0.021 (95% CI -0.419 to 0.074, I² = 57.9% p= 0.093). It should be noted that the p-value for the z-score was calculated using the fixed effects model. Since there was heterogeneity present in this subgroup, the random effects model was used to test the significance of the results, because it takes into account the between-study variance. The random effects model had a broader CI, which was not statistically significant. Finally, there were 3 studies that did not specify the location of uveitis; they had a WMD of -0.081 (95% CI -0.192 to 0.031 p=0.157, I²=0%). Heterogeneity was found in 1 of the 5 categories, which was the combination of locations, which showed an I² measure of 57.8%, but it was not significant. This can been seen in Figure 8.

6.4.4.3 Subgroup Analysis by Treatment

Fourteen studies that used antimetabolites as the primary treatment indicated that patients had a statistically significant improvement in vision, with a WMD of -0.131 change in logMAR, p=0.001 (95% CI -0.211 to -0.050, I²=0%). Fifteen studies where patients were given T-cell inhibitors as the primary treatment showed a statistically significant improvement in vision, with a WMD of -0.109, p=0.001 (95% CI -0.172 to -0.045, I²=0%, p=0.680). In one study, in which patients were given an alkylating agent, the
WMD was -0.146, p=0.497 (95% CI -0.567 to 0.275). Two studies, where patients were given a combination of various immunosuppressive treatments had a WMD of -0.050, p=0.497 (95% CI -0.163 to 0.064, 0% p=0.328). This can been seen in Figure 9.

6.4.4.4 Subgroup Analysis by Previous Treatment

All 3 categories: steroids, not specified, and a combination of steroids and immunomodulatory treatment demonstrated a statistically significant improvement in vision after primary treatment was given. However, there was no heterogeneity in any of the categories. Fifteen studies that had given only steroids as the previous treatment had a WMD of -0.120, p=0.002 (95% CI -0.198 to -0.042, $I^2=0\%$). Five studies within unspecified previous treatments had a WMD of -0.100, p=0.018 (95% CI -0.157 to -0.018, $I^2=0\%$), while the treatments with steroids plus various immunosuppressive treatment had a WMD of -0.120, p=0.008 (95% CI -0.209 to -0.031, $I^2=0\%$). This can been seen in Figure 10.
Figure 5: Pooled random effects (D+L) Meta-analysis of change in logMAR for idiopathic uveitis patients given immunosuppressive treatments (IMM)
Figure 6: Sensitivity Analysis (Removal of 6 studies): pooled random effects (D+L) meta-analysis of change in logMAR for idiopathic uveitis patients given immunosuppressive treatments (IMM)
Figure 7: Fixed effects (I+V) subgroup analysis by age examining the change in logMAR for idiopathic uveitis patients given immunosuppressive treatments (IMM)
Figure 8: Fixed effects (I+V) subgroup analysis by location of disease examining the change in logMAR for idiopathic uveitis patients given immunosuppressive treatments (IMM)
Figure 9: Fixed effects (I+V) subgroup analysis examining the change in logMAR for idiopathic uveitis patients given the different immunosuppressive treatment (IMM) classes.
Figure 10: Fixed effects (I+V) subgroup analysis by previous treatments examining the change in LogMAR for idiopathic uveitis patients given immunosuppressive treatments (IMM)
Table 39: Summary of Pooled Meta-analysis and Subgroup Analysis examining the change in logMAR for treating idiopathic patients with immunosuppressive treatments

<table>
<thead>
<tr>
<th>Meta-analysis on:</th>
<th>Subgroup</th>
<th>Number of Studies*</th>
<th>WMD (95% CI)</th>
<th>Significance test of WMD = 0 (p-value)</th>
<th>Test of heterogeneity, I^2 (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled</td>
<td>--</td>
<td>32</td>
<td>-0.107 (-0.152 to -0.061)</td>
<td>z = 4.61 (p = 0.0)</td>
<td>0% (p = 0.987)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>--</td>
<td>24</td>
<td>-0.107 (-0.153 to -0.062)</td>
<td>z = 4.61 (p = 0.0)</td>
<td>0% (p = 0.854)</td>
</tr>
<tr>
<td>Age</td>
<td>Greater than or equal to 18</td>
<td>22</td>
<td>-0.147 (-0.208 to -0.087)</td>
<td>z = 4.79 (p = 0.0)</td>
<td>0% (p = 0.990)</td>
</tr>
<tr>
<td></td>
<td>Less than 18</td>
<td>10</td>
<td>-0.053 (-0.122 to 0.015)</td>
<td>z = 1.52 (p = 0.128)</td>
<td>0% (p = 0.954)</td>
</tr>
<tr>
<td>Previous Treatment</td>
<td>Immunmodulatory</td>
<td>9</td>
<td>-0.120 (-0.209 to -0.031)</td>
<td>z = 2.64 (p = 0.008)</td>
<td>0% (p = 0.859)</td>
</tr>
<tr>
<td></td>
<td>Steroids</td>
<td>15</td>
<td>-0.120 (-0.198 to -0.042)</td>
<td>z = 3.03 (p = 0.002)</td>
<td>0% (p = 0.962)</td>
</tr>
<tr>
<td></td>
<td>Not Specified</td>
<td>5</td>
<td>-0.087 (-0.157 to -0.015)</td>
<td>z = 2.37 (p = 0.018)</td>
<td>0% (p = 0.482)</td>
</tr>
<tr>
<td>Location of Disease</td>
<td>Panuveitis</td>
<td>5</td>
<td>-0.100 (-0.218 to 0.018)</td>
<td>z = 1.65 (p = 0.098)</td>
<td>0% (p = 0.998)</td>
</tr>
<tr>
<td></td>
<td>Combination of Locations</td>
<td>3</td>
<td>-0.172 (-0.419 to 0.074)</td>
<td>z = 2.31 (p = 0.021)</td>
<td>57.9% (p = 0.093)</td>
</tr>
<tr>
<td></td>
<td>Posterior Uveitis</td>
<td>10</td>
<td>-0.057 (-0.143 to 0.029)</td>
<td>z = 1.31 (p = 0.191)</td>
<td>0% (p = 0.996)</td>
</tr>
<tr>
<td></td>
<td>Intermediate Uveitis</td>
<td>9</td>
<td>-0.146 (-0.226 to -0.066)</td>
<td>z = 3.57 (p = 0.0)</td>
<td>0% (p = 0.677)</td>
</tr>
<tr>
<td></td>
<td>Not Specified</td>
<td>3</td>
<td>-0.081 (0.194 to 0.031)</td>
<td>z = 1.42 (p = 0.157)</td>
<td>0% (p = 0.962)</td>
</tr>
<tr>
<td>Primary Treatment Class</td>
<td>Anti-Metabolites</td>
<td>14</td>
<td>-0.131 (-0.211 to -0.050)</td>
<td>z = 3.18 (p = 0.001)</td>
<td>0% (p = 0.999)</td>
</tr>
<tr>
<td></td>
<td>T-cell Inhibitors</td>
<td>15</td>
<td>-0.109 (-0.172 to -0.045)</td>
<td>z = 3.36 (p = 0.001)</td>
<td>0% (p = 0.680)</td>
</tr>
<tr>
<td></td>
<td>Combination of Treatments</td>
<td>2</td>
<td>-0.050 (-0.163 to 0.064)</td>
<td>z = 0.86 (p = 0.392)</td>
<td>0% (p = 0.328)</td>
</tr>
<tr>
<td></td>
<td>Alkylating Agents</td>
<td>1</td>
<td>-0.146 (-0.567 to 0.275)</td>
<td>z = 0.68 (p = 0.497)</td>
<td>(only 1 study)</td>
</tr>
</tbody>
</table>

Legend: WMD = Weight Mean Difference, *Number of studies including the independent subgroups in some studies (n=32)
6.4.5 Meta-regression

Even though there was no heterogeneity found in the pooled analysis, meta-regression was still undertaken, as it was predefined on the onset of the study. There were 8 univariate random effect meta-regressions that we conducted. Furthermore, since there was heterogeneity found, which was found to be not significant, it was wise to have undertaken a meta-regression. As seen in Table 40 below, none of the pre-specified covariates were found to be significant and no heterogeneity was found in any of the covariates (as can be seen with the 0% $I^2$ value).
Table 40: Results from fitting 8 random effect univariate meta-regression models that examined the effects of covariates on treatment effectiveness measure, logMAR

<table>
<thead>
<tr>
<th>Meta-regression on:</th>
<th>Covariate</th>
<th>Regression Coefficients (95% CI)</th>
<th>P-value</th>
<th>Joint P-value</th>
<th>I^2</th>
<th>Adjusted R^2</th>
<th>T^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of Study</td>
<td>North America (1) vs. Other (0)</td>
<td>-0.0410 (-0.145 to 0.0627)</td>
<td>0.426</td>
<td>--</td>
<td>0%</td>
<td>.%</td>
<td>0.0067</td>
</tr>
<tr>
<td>Year of study</td>
<td>After 2005 (1) vs. before or on 2005 (0)</td>
<td>0.0389 (-0.0578 to 0.136)</td>
<td>0.364</td>
<td>--</td>
<td>0%</td>
<td>.%</td>
<td>0</td>
</tr>
<tr>
<td>Type of Study</td>
<td>Observational (1) vs. RCT (0)</td>
<td>0.0373 (-1.36 to 0.210)</td>
<td>0.663</td>
<td>--</td>
<td>0%</td>
<td>.%</td>
<td>0</td>
</tr>
<tr>
<td>%Female</td>
<td>%Female Distribution</td>
<td>0.000667 (-0.0285 to 0.00418)</td>
<td>0.700</td>
<td>--</td>
<td>0%</td>
<td>.%</td>
<td>0</td>
</tr>
<tr>
<td>Mean Age</td>
<td>Greater than or equal to 18 (1) vs. Less than 18 years old (0)</td>
<td>-0.0941 (-0.189 to 0.0132)</td>
<td>0.053</td>
<td>--</td>
<td>0%</td>
<td>.%</td>
<td>0</td>
</tr>
<tr>
<td>Previous Treatment</td>
<td></td>
<td></td>
<td>0.751</td>
<td>0%</td>
<td>.%</td>
<td>0.00139</td>
<td></td>
</tr>
<tr>
<td>Immunmodulatory*</td>
<td></td>
<td></td>
<td></td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>0.00658 (-0.129 to 0.142)</td>
<td>0.922</td>
<td>0%</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Specified</td>
<td>0.0436 (-0.0916 to 0.180)</td>
<td>0.515</td>
<td>0%</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of Disease</td>
<td></td>
<td></td>
<td>0.531</td>
<td>0%</td>
<td>.%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Panuveitis</td>
<td>0.0774 (-0.1223 to 0.278)</td>
<td>0.435</td>
<td>0%</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
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<tr>
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*Not included due to collinearity
6.4.6 Publication Bias

Publication bias was assessed using Duval and Tweedie’s trim and fill method. Once the algorithm was complete there was no trimming to be done, however, there was 1 study that was filled in, which can be seen in Figure 11 in the study that has a square around it. This indicates that a study was added to make the funnel plot symmetrical and less biased.

![Filled funnel plot with pseudo 95% confidence limits](image)

Figure 11: Publication bias, with Duval and Tweedie (2000) Method: Funnel plot with pseudo 95% confidence limits
Chapter 7

7 Discussion

7.1 Systematic Review

This study is unique in that it is the first systematic review and meta-analysis conducted on immunosuppressive treatments given to non-infectious idiopathic uveitis patients (averaging 78% of the patients having idiopathic uveitis with all the studies combined). There were 2251 citations screened using the inclusion/exclusion criteria. The 45 studies included in the systematic review were found to have moderate quality of evidence according to the Downs and Black checklist. The 45 studies were divided into different immunosuppressive treatment groups.

Also, most studies were done on the subjects that analyzed both eyes of each patient rather than each eye individually. Issues with measuring per eye could lead to discrepancies and heterogeneity, if they do not correlate the outcome between eyes. Recently, Multicenter Uveitis Steroid Treatment (MUST) Trial Research Group (2015)\(^97\) was very careful to make this distinction accounting for the likely correlation in responses between eyes from subjects with disease in both eyes. This distinction needs to be there or else it could lead to heterogeneity if not accounted for.

The patient and study characteristics were very similar among the various immunosuppressive treatment groups, with the antimetabolites having the greatest number of studies (23) and a sample size comprising of 1451 patients. The treatment group with the second greatest number was the inhibitors of T-lymphocyte signalling, with 15 studies and 772 patients. Given their similarity in size, these 2 treatment groups could be compared fairly but are limited to descriptive statistics as no statistical inference was carried out. The year, the type, and the location of where the studies were conducted were similar across the different treatment groups. In most treatment groups the frequency of patients that had idiopathic uveitis were similar along with factors such as age. In most studies, location of uveitis in patients was almost evenly divided between posterior uveitis and intermediate uveitis, and majority were idiopathic in nature. This
enabled a systematic review to focus on studies that were specific to our question, and allowed for as much homogeneity that could be facilitated with the data available.

The antimitabolite treatment group showed the most positive effect on VA: in 5 studies with MTX, VA improved or maintained in 88% of the patients with a sample size of 526 patients, while in 10 studies with 271 patients given MMF, VA improved or maintained in 85.5% of patients. In 4 studies with 474 patients given CsA, which belonged to the inhibitors of T-cell signalling treatment group, VA improved or maintained in 59.5% of the patient population. In 1 study, 81% of patients who received TAC, another treatment belonging to the same treatment group, improved or maintained VA. These findings suggest that MTX and MMF, which belong to the antimitabolite treatment group, are the most effective in treating uveitis patients.

Inflammation grade, which is a more direct measure of improvement from uveitis, also maintained or improved with antimitabolite treatment, with MTX having a positive effect on 72.5% of the patient population in 2 studies, and MMF on 77.5% of the patient population in 7 studies. However, the frequencies presented cannot be used as the sole means to detect efficacy, as a more analytical approach should be used to assess efficacy of the different treatment groups. But, in past narrative reviews, due to the heterogeneity in patient types and outcomes measures, no real comparison was ever done. While our systematic review of smaller patient groups and different treatments allows these values to be compared descriptively, definitive conclusions are difficult to make.

Discontinuation rates were low for both MTX and MMF, with lack of efficacy as the main reason for the treatments being discontinued. MTX contained 6 studies, with 13% to 48% of patients discontinuing treatment, while the 5 MMF studies indicated that 12% to 35% of patients discontinued treatment. CsA was discontinued mainly due to intolerance and side effects (specifically renal toxicity). This accounted for 11% to 30% of patients discontinuing in the 5 studies that used CsA. The RCT with TAC indicated that treatment failure lead to discontinuation of treatment in 50% of patients. Lack of efficacy was another reason some of the patients that were given TAC were removed from the study. MTX and MMF caused mild adverse events in about 14% of patients.
while CsA and TAC had a greater number of patients for whom adverse events could be harmful, such as renal toxicity. This corresponds with many studies that suggest CsA can cause severe side effects, and larger doses of CsA can be more harmful to patients.

7.2 Quality Assessment

The quality of the studies was examined using the Downs and Black checklist, which indicated that there were some low quality papers present (10%). However, the majority of the papers were of moderate quality. All studies were included in the meta-analysis and systematic review. The systematic review also indicated that many of the studies were not of high quality, as evident from the literature search of the systematic review.

The methodological quality of included studies in the meta-analysis was at least moderate. As discussed in section 5.6, the median score of observational studies being 48%, indicated that the quality of the studies were “poor to moderate”. However, the internal validity of the observational studies was very poor, with 19% of studies having scored a “yes” in the validity section. This suggests that there is a bias in intervention measures for the primary outcome. This was either due to the fact that the analysis related to the measure of choice for the VA scale or alternatively, how they analyzed the patients’ data, such as per eye or subject level. This could indicate that there was in fact heterogeneity related to our meta-analysis, when comparing intervention groups and the outcomes. However, most of these validity questions were specific to randomized control trials, and having case series and cohort studies could limit how interventions are dealt with and measured, but does not mean that it would cause major discrepancies that would hinder our results.

A meta-regression of the types of studies were compared (RCTs and observational studies), and although nothing significant was found, there was a slight difference between the change in logMAR between the 2 groups, with RCTs demonstrating a more positive effect on logMAR post-treatment. However, it is important to note that there was no heterogeneity between the 2 groups ($1^2 = 0\%$). This further strengthened our confidence in the results.
7.3 Meta-analysis and Subgroup Analysis

There were 26 studies included in the meta-analysis, dealing with change in logMAR, once idiopathic uveitis patients are given immunosuppressive treatments. Of these, 5 studies did not include either pre-treatment or post-treatment logMAR, but did include the change in logMAR, which was added postoperatively by using the mean pre-logMAR calculated by the 20 studies that were present in the meta-analysis. Also, the pre- and post-SD was missing from 1 study, so we had to use the highest SD given in 1 of the 26 studies, which allowed for a conservative value for the missing SD. The studies with missing pre- and post- data did in fact demonstrate a change in logMAR and the respective SD, so we did not make up values, but used the information provided and extrapolated the data, which is advised when partial data is missing.

Some of the studies had independent subgroups (ie, 1 study included a subset of patients treated with antimetabolites and another subset of patients treated with T-cell inhibitors), which were included as individual studies, increasing the total study count to 32 studies. From these 32 studies, 78.3% indicated a reduced logMAR (improved vision) when patients were given immunosuppressive treatments. Using the weighted mean difference in the overall use of treatment of any kind indicated a reduction in logMAR of -0.11, which was significant (p=0). This suggests that there was an improvement in vision with a change in 1.5 lines or -0.11 logMAR. Generally speaking a clinically relevant change in vision may be described as 2 lines or -0.2 logMAR.

The sensitivity analysis, when the studies with missing data were removed and the analysis was run again on only 24 studies, supported these results as well. Even with the removal of those studies, there was no difference in the overall effect, which was still significant. There was also no difference in heterogeneity. These results support results found in the existing literature, which indicate that immunosuppressive treatments are effective in treating patients with inflammatory eye disease.

While our results indicated there was no heterogeneity, it was not significant. To better understand this, we conducted a subgroup and meta-regression to verify that heterogeneity was not present and to evaluate whether any of the subgroup categories
were more positively or negatively affected by the immunosuppressive treatment (for example, did treatment affect different age groups differently, or did location of the disease have an impact on effect size).

The results from the subgroup analysis for age indicated that individuals greater than or equal to 18 years of age were affected more positively by the treatment than patients under 18 years of age. Patients in the former group also demonstrated a statistically significant change in logMAR of -0.147 with a p-value of 0. The heterogeneity in patients greater than 18 years was 0%, which indicates that the different treatment groups had a similar effect on this patient subgroup. This suggests that any immunosuppressive treatment is likely to be effective for patients older than 18 years, and that the results are statistically significant. In contrast, even though patients younger than 18 years experienced improvement in vision, the improvement was not statistically significant. In this thesis, 10 of the studies we examined contained patients below 18 years of age. Six studies used antimetabolites, and they indicated that antimetabolites may not be appropriate for patients younger than 18 years. (Most of these patients were JIA with uveitis, and some were uveitis patients with no JIA involved, which could also explain the non-significance).

Results from the subgroup analysis of previous treatment given to patients was also important, as patients that were given just steroids before receiving the treatment of choice had a statistically significant positive change in logMAR (WMD= -0.120, p=0.002 with I^2=0%). This was also seen in patients given steroids and other immunosuppressive treatments before receiving the treatment of choice (WMD= -0.120 p=0.008). Furthermore, studies that did not specify also showed a statistically significant positive change. This could be explained by the fact that no matter which treatment they were previously given, what mattered at the end was the impact the primary treatment had on patients.

Subgroup analysis by location indicated that the only category that contains heterogeneity is the combination of locations patient group (I^2=57.9%, p=0.093). This could be explained by the fact that there were 3 different groups of patients within a study, and
since there were only 3 studies in the subgroup, it could have resulted in the heterogeneity seen in the subgroup analysis. Also, interestingly, intermediate uveitis was shown to be the group most effectively treated by immunosuppressive treatment, and it was statistically significant (WMD= -0.146, p=0). This means that patients with intermediate uveitis have a better chance of responding to treatment from any of the treatment groups, more so than the other 2 locations. However, as is noted in Figure 8, there were 6 studies where intermediate uveitis patients were given antimetabolites, whereas patients with posterior uveitis were mainly given T-cell inhibitors. This suggests that antimetabolite treatment may play a role in why intermediate uveitis patients demonstrated a greater change in logMAR, and thus improvements in vision, or it may suggest that it is easier to treat patients with intermediate uveitis than those with posterior uveitis.

Subgroup analysis by treatment found that patients given antimetabolites were more positively (WMD= -0.131, p=0.001) treated then patients given inhibitors of T-cell signalling (WMD= -0.109, p=001). This finding is similar to descriptive outcomes found in the systematic review with frequencies, which indicated that antimetabolites are more effective in maintaining or improving VA in patients. However, comparing the pre- and post-logMAR treatment is a more accurate measure of the number of patients who got better after treatment was administered. This supports the subgroup analysis of location of disease discussed above, as intermediate uveitis patients also responded positively when treated with immunosuppressive treatments, and since they were given antimetabolites, it seems fair to conclude that antimetabolites were more effective overall than other treatments. However, it is interesting to note that both subgroup treatment groups experienced a statistically significant positive effect on vision. This suggests that being given either of the 2 treatments is beneficial to patients, with antimetabolites having a slight advantage in treating patients, especially those with intermediate uveitis. Since the other 2 treatment groups only contained 1 to 2 studies, it is not fair to compare those groups.
7.4 Meta-regression

With the meta-regression, although there was no heterogeneity to begin with, some doubt remained because it was not statistically significant in the pooled meta-analysis. After running the meta-regression, none of the covariates were found to be associated with change in logMAR. Furthermore, there was no heterogeneity found in the regression models with all the covariates. We also determined joint p-values, as the meta-regression was done with multiple categories with a covariate, for example, primary treatment had a joint p-value of 0.744, which indicates that there is very little evidence the change in logMAR differs among the 4 categories. The same conclusion can be drawn for all the covariates that we examined. This suggests that the heterogeneity of 0% found in the pooled analysis was accurate to a certain extent, since the goal of a meta-regression is to investigate the heterogeneity between results of multiple studies and one or more characteristics of a study can alter that heterogeneity. Since no heterogeneity was found, meta-regression was not necessary for this study, but it added a layer of further understanding by indicating that heterogeneity was not present.

Finally, although it was stated in the methods that a permutation test would be done, since none of the covariates had a significant p-value, a permutation test was not needed.

7.5 Publication Bias

For publication bias, we used the trim and fill method, as mentioned earlier. Three iterations were needed, which enabled us to identify and fix the asymmetry by adding 1 extra study to balance out the others, as can be seen in Figure 11. The addition of the extra study made the WMD = -0.110, 95% CI -0.155 to -0.065.

As can be seen in the funnel plot, everything is within symmetry. This suggests that there were no extreme positive studies that could have caused deviation. However, imputation was required to create more symmetry. In other words, our selection of studies may have been unbiased and mainly symmetrical with regards to the underlying common effect, but we used the trim and fill method to be certain that any existing asymmetry was addressed.
In conclusion, this study found that there was no heterogeneity in the pooled analysis, nor was there any heterogeneity in the subgroup analysis or the meta-regression. This indicates that the population group was fairly homogeneous and could be compared from one study to another. Another interesting take away is that all treatments seemed to be effective at treating uveitis, with antimetabolites and T-cell inhibitors reporting statistically significant results. However, antimetabolites were more effective at treating patients, demonstrating a greater change in logMAR then T-cell inhibitors.

7.6 Strengths

Meta-analysis is a powerful tool that can assist researchers when an overwhelming amount of information is present, even when the field of study is quite narrow. However, there can be drawbacks to conducting a meta-analysis, and it can be controversial if not done correctly. Methodology is the most important attribute in both a systematic review and a meta-analysis. Even a slight deviation or violation of the methods could lead to misleading results and bias.

Our study adhered to all possible guidelines and rules of thumb from the search strategy in the way our meta-regression was done, with consideration of all caveats. All work was done very carefully, from the search strategy, to the article capturing and screening, to the data abstraction, to the analysis. Careful analysis of the data was important to ensure reliable results. The Cochrane Collaboration and the PRISMA guidelines were followed to ensure that the meta-analysis was completed and reported with precision (see Appendix A and B).

This is the first systematic review and meta-analysis undertaken on the treatments given to patients that specifically have non-infectious idiopathic uveitis. We screened 2251 citations using the inclusion/exclusion criteria. Unlike previous narrative and systematic reviews, our systematic review developed a meticulous search strategy with the help of an information specialist. There were 6 scientific databases used to collect relevant articles, and a comprehensive search of grey literature was also done. Strict inclusion/exclusion criteria were developed specific to our research question, and the studies were independently screened by 2 reviewers, in order to reduce potential bias.
The inclusion/exclusion criteria were created to ensure homogeneity in both the studies and the patient population. The patient population was homogenous, according to the following criteria: primary treatment given to the patients was orally administered in all studies, studies were limited by the type of previous treatments given, the locations of uveitis were mainly intermediate and posterior uveitis, and the disease was specific to idiopathic uveitis. The heterogeneity from the patient population was only in the primary treatment given to the patients.

Unlike previous reviews, our study also used a quality assessment tool, the Downs and Black checklist. The checklist is one of the only validated checklists for methodological quality of observation studies. We used the checklist for all 45 studies, of which, the 28 used in the meta-analysis were moderate studies, with some RCTs as well. This suggests that the studies that remained for our analysis were strong enough to ensure the integrity of the results.

Alongside the systematic review, it was very important for the meta-analysis to adhere to the strict guidelines and accurately conduct the analysis. We anticipated that the pooled meta-analysis would have heterogeneity because all the studies were pooled together. However, there was a specific factor in the heterogeneity, which was the primary treatment, and therefore we needed other tests to investigate where the heterogeneity came from. We used subgroup analysis and meta-regression to test and quantify the heterogeneity. All precautions and rules were followed to ensure the integrity of the results. The subgroup analysis was conducted even with the subgroups that had fewer than 5 studies. Another method used to investigate the heterogeneity and to bypass the subgroup analysis problem was a meta-regression. Here, while many methods were considered, the best method for our meta-analysis was the Knapp and Hartung univariate meta-regression. Finally, we also planned to conduct a permutation test to ensure no false negative p-values were present in the initial test.

7.7 Limitations

Even though publication bias was found through the trim and fill method, with very minimal changes, there were no non-English studies used in our study, which is one
limitation that could lead to publication bias. Future studies should attempt to include non-English studies.

The quality of the 45 studies used in this systematic review was mild to moderate, only stating frequencies of improvements to visual acuity and inflammation grade, but otherwise not having much statistical basis. However, the 28 studies that we used for the meta-analysis contained more robustness in their methodology, which helped to compensate for the overall quality of the 45 studies.

Some of the data that was collected in the extraction sheets was not used in the analysis, in particular, the dosage, which could have played an important role in understanding the heterogeneity. However, dosage was left out because the dosages for treatment groups could not be compared, as different treatment groups required different dosages. Another limitation is that some of the subgroups contained fewer than 5 studies, which can cause bias. Generally, small subgroups such as this should not be compared to other subgroups, however, using meta-regression on these subgroups helped to alleviate the issue when assessing the data.

Also, we could have had methodological heterogeneity with our primary outcome. It has been found that there is a clear correlation between the scales measuring VA. The regression analysis revealed a significant correlation between the visual acuity scores on the 2 charts ($R^2 = 0.8839$) with a slope significantly different from 1 ($P < .0001$). However, it is also been noted that the Snellen method is not as reliable as the logMAR method when measuring for VA. This could lead to heterogeneity as our study had a variation on measuring VA. Though we standardized the scales to logMAR, the initial method used to measure VA could have led to methodological heterogeneity. Future studies should test to see whether the difference in scales resulted in different results, using either a subgroup or meta-regression analysis.

Also, important to note is that even though most studies conducted on the subject level, it should be important to ensure that the methodology used by the studies allowed for correlation if there was two observations done per individual. Thus, in future studies, we should be stricter on the methodology of the studies, so we can ensure that studies that do
report two observations per individual, account for correlation and thus would lead to less error within the study and higher quality of the study for internal validity.

Another limitation is that heterogeneity was not pooled by treatment group, because there were not enough studies in each treatment group to conduct a subgroup analysis or meta-regression on each treatment group separately. When subgroup analysis or meta-regression was conducted it was conducted on the pooled data. However, due to the lack of studies, we were unable to conduct more specific analysis, such as examining the heterogeneity of the covariates or subgroups that were examined in the pooled data, for each primary treatment group. This may limit the interpretation of the results and introduce complications regarding the main question this thesis wanted to answer.

In addition to the above, no analysis was conducted on the outcome of inflammation grade, even though it is a better measure of improvement in the severity of uveitis. Again, this was a result of not having enough studies containing the information necessary to conduct a meta-analysis on this outcome. While this reduces the applicability of the results, it is a good starting point.

Finally, one of the most significant limitations of a meta-analysis is the fact that any results obtained from the subgroup analysis and meta-regression are observational in nature. Any statistically significant or non-statistically significant result cannot be used to draw any concrete conclusions, but could be used to make an observation. This is important to keep in mind since power to detect heterogeneity in effect sizes or between covariates or subgroups is very low. In other words, failure to obtain a statistically significant difference among subgroups should never be interpreted as evidence that the effect is the same across subgroups. The same can be said for obtaining a statistically significant result. Simple failure to obtain a statistically significant effect for a covariate should never be interpreted as evidence that there is no relationship between the covariate and the effect size.
7.8 Possibilities for future research

In future studies, there are a few elements that can be taken into consideration to ensure better results that are more viable for converting to policy. One is the inclusion of non-English studies. If we had included studies from other languages, it would have increased our meta-analysis by 29 studies. Another is the inclusion of biologics as a treatment group. Finally, our study did not include an analytical comparison of adverse events. Future studies should include this element, which would facilitate a deeper understanding about the effectiveness of different treatments. In addition to including the above elements, future studies should also conduct a cost-effectiveness analysis, which is a key element for creating policy. Including a cost-effectiveness model, done in accordance with CUS and COS, would be the final step in ensuring a comprehensive study that can be used to inform policy and further our understanding about off-label treatments and their ability to treat uveitis patients.

7.9 Conclusion

This systematic review and meta-analysis were conducted with the utmost care and accuracy. Idiopathic non-infectious uveitis patients that received 1 of 3 different treatment groups were the primary patient population this study examined. There were specific criteria used to determine which studies were included in the systematic review and meta-analysis. This study helped to paint a better picture about the different treatments administered to patients with non-infectious idiopathic uveitis. All treatments were found to be effective in the pooled analysis, with a logMAR of -0.11. Furthermore, there was an indication in the subgroups analysis that treatment was particularly efficacious in patients over 18, patients with intermediate uveitis, patients treated with antimetabolites, and patients pretreated (usually with steroids). Finally, there was minimal heterogeneity present, which was explained in the subgroup analysis. Future studies, especially those that include a cost-effectiveness analysis, will allow us to draw better conclusions about the most effective treatments for non-infectious idiopathic uveitis.
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Appendices

Appendix A: Meta-analysis of Observational Studies in Epidemiology (MOOSE) Checklist

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<td>Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)</td>
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<td>Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)</td>
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<td>Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results</td>
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<tr>
<td>Assessment of heterogeneity</td>
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<td>Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated</td>
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Appendix B: Preferred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) guidelines

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<tr>
<td><strong>TITLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td></td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>ii</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>33-34</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>52</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.</td>
<td>--</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td>56-57</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>55-56</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>152-157</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>52-53</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>52-55</td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.</td>
<td>53-55, 158</td>
</tr>
<tr>
<td><strong>Risk of bias in individual studies</strong></td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Summary measures</strong></td>
<td>13</td>
<td>State the principal summary measures (eg, risk ratio, difference in means).</td>
<td></td>
</tr>
<tr>
<td><strong>Synthesis of results</strong></td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I²) for each meta-analysis.</td>
<td></td>
</tr>
<tr>
<td><strong>Risk of bias across studies</strong></td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).</td>
<td></td>
</tr>
<tr>
<td><strong>Additional analyses</strong></td>
<td>16</td>
<td>Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td></td>
</tr>
</tbody>
</table>

### RESULTS

| **Study selection** | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. |
| **Study characteristics** | 18 | For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations. |
| **Risk of bias within studies** | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). |
| **Results of individual studies** | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. |
| **Synthesis of results** | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. |
| **Risk of bias across studies** | 22 | Present results of any assessment of risk of bias across studies (see Item 15). |
| **Additional analysis** | 23 | Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]). |

### DISCUSSION

<p>| <strong>Summary of evidence</strong> | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers). |
| <strong>Limitations</strong> | 25 | Discuss limitations at study and outcome level (eg, risk of bias), and at review-level (eg, incomplete retrieval of identified research, reporting bias). |</p>
<table>
<thead>
<tr>
<th>Table: Conclusions</th>
<th>26</th>
<th>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</th>
<th>130-131</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUNDING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Funding</strong></td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.</td>
<td>--</td>
</tr>
</tbody>
</table>
Appendix C: Search Strategies

MEDLINE (Ovid)
Timespan:
Ovid MEDLINE(R) 1946 to July Week 1, 2012
Ovid MEDLINE(R) Daily Update July 13, 2012
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 13, 2012

SEARCH STRATEGY (Blue = Keywords / Red = MeSH)

1 Uveitis or "Ocular inflammat$" or "Intraocular inflammat$"
2 Uveitis/ OR intermediate uveitis/ OR Uveitis, Anterior/ OR Uveitis, Posterior/
3 1 OR 2
   (Immunosuppress$ or immunomodulat$) ADJ2 (agent$1 or treatment$1 or
   drug$1 or therap$)
4 Immunosuppressive Agents/ or Immunosuppression/ or Immunologic
5 Factors/
6 4 OR 5
   Antimetabolite$ or Azathioprine or Methotrexate or "Mycophenolic Acid" or
   Alkylating Agent$ or Cyclophosphamide or Chlorambucil or Cyclosporine or
   Tacrolimus or Sirolimus or Rapamycin or amethopterin OR "Mycophenolate
   Mofetil" OR cytophosphane OR FK-506 OR fujimycin OR Imuran OR Azasan
   OR rheumatrex OR cellcept OR trexall OR myfortic OR cytoxan OR endoxan
   OR cytoxan OR neosar OR procytox OR revimmune OR chlorambucil or
   leukeran or "calcineurin inhibitor$" or gengraf or neoral or sandimmune or
   7 prograf or advagraf or protopic or rapamune
   Antimetabolites/ or Azathioprine/ or Methotrexate/ or Mycophenolic Acid/
   or Alkylating Agents/ or Cyclophosphamide/ or Chlorambucil/ or calcineurin
   inhibitor/ or Cyclosporine/ or Tacrolimus/ or Sirolimus/ or Rapamycin/
8 7 OR 8
9 7 OR 8
10 3 AND (6 OR 9)

Results = 1822

Explanation of Syntax Used:
- the dollar sign ($) finds all variations of word endings (i.e, comput$ finds computer, computing, etc.)
- the number sign (#) finds words that may appear with or without an extra letter (i.e, computer# finds computer or computers)
- the Adjacency Operator (ADJ) searches for 2 or more words that appear within a specified number of words (or fewer) of each other and in any order (i.e, "tax ADJ5 reform" would find instances of "tax reform" as well as "reform of income tax")
**EMBASE (Ovid)**
Timespan: Embase 1980 to 2012 Week 28

**SEARCH STRATEGY (Blue = Keywords / Red = EMTREE Terms)**

1. Uveitis or "Ocular inflammat$" or "Intraocular inflammat$"
2. Uveitis/ OR intermediate uveitis/ OR Uveitis, Posterior/
3. 1 OR 2
   (Immunosuppress$ or immunomodulat$) ADJ2 (agent$1 or treatment$1 or drug$1 or therap$)
4. Immunosuppressive Agent/ or Immunosuppressive Treatment/ or immunomodulating agent/
5. 4 OR 5
6. Antimetabolite$ or Azathioprine or Methotrexate or "Mycophenolic Acid" or Alkylating Agent$ or Cyclophosphamide or Chlorambucil or Cyclosporine or Tacrolimus or Sirolimus or Rapamycin or amethopterin OR "Mycophenolate Mofetil" OR cytophosphane OR FK-506 OR fujimycin OR Imuran OR Azasan OR rheumatrex OR cellcept OR trexall OR myförtic OR cytoxan OR endoxan OR cytoxan OR neosar OR procitox OR revimmune OR chlorambucil or leukeran or "calcineurin inhibitor$" or gengraf or neoral or sandimmune or prograf or advagraf or protopic or rapamune
7. Antimetabolites/ or Azathioprine/ or Methotrexate/ or Mycophenolic Acid/ or Alkylating Agents/ or Cyclophosphamide/ or Chlorambucil/ or Cyclosporine/ or Tacrolimus/ or Sirolimus/ or Rapamycin/
8. 7 OR 8
9. 7 OR 8
10. 3 AND (6 OR 9)

**Results = 3786**

**Explanation of Syntax Used:**
- the dollar sign ($) finds all variations of word endings (i.e., comput$ finds computer, computing, etc.)
- the number sign (#) finds words that may appear with or without an extra letter (i.e, computer# finds computer or computers)
- the Adjacency Operator (ADJ) searches for 2 or more words that appear within a specified number of words (or fewer) of each other and in any order (i.e, "tax ADJS reform" would find instances of "tax reform" as well as "reform of income tax")
CINAHL (EBSCO)
Timespan: 1982-present

SEARCH STRATEGY (Blue = Keywords / Red = CINAL Subject Terms)

1  Uveitis or "Ocular inflammat*" or "Intraocular inflammat*" (MH "Uveitis") OR (MH "Uveitis, Anterior") OR (MH "Uveitis, Intermediate") OR (MH "Uveitis, Posterior")
2  1 OR 2
3  (Immunosuppress* or immunomodulat*) N2 (agent# or treatment# or drug# or therap*)
4  (MH "Immunosuppressive Agents") OR (MH "Immunosuppression") OR (MH "Immunologic Factors")
5  4 OR 5
6  4 OR 5
7  Antimetabolite# or Azathioprine or Methotrexate or "Mycophenolic Acid" or Alkylating Agent# or Cyclophosphamide or Chlorambucil or Cyclosporine or Tacrolimus or Sirolimus or Rapamycin or amethopterin OR "Mycophenolate Mofetil" OR cytophosphane OR FK-506 OR fujimycin OR Imuran OR Azasan OR rheumatrex OR cellcept OR trexall OR myfortic OR cytoxan OR endoxan OR neosar OR procytox OR revimmune OR chlorambucil or leukeran or "calcineurin inhibitor#" or gengraf or neoral or sandimmune or prograf or advagraf or protopic or rapamune (MH "Antimetabolites") OR (MH "Azathioprine") OR (MH "Methotrexate") OR (MH "Mycophenolate Mofetil") OR (MH "Mycophenolic Acid") OR (MH "Cyclophosphamide") OR (MH "Alkylating Agents") OR (MH "Cyclosporine") OR (MH "Sirolimus")
8  7 OR 8
9  7 OR 8
10 (3) AND (6 OR 9)

Results = 89

Explanation of Syntax Used:
- the asterisk sign (*) finds all variations of word endings (i.e, comput* finds computer, computing, etc.)
- the number sign (#) finds words that may appear with or without an extra letter (i.e, computer# finds computer or computers)
- the Near Operator (N ) searches for 2 or more words that appear within a specified number of words (or fewer) of each other and in any order (i.e, "tax N5 reform" would find instances of "tax reform" as well as "reform of income tax")
SEARCH STRATEGY

1. Uveitis or "Ocular inflammat$" or "Intraocular inflammat$"
   (Immunosuppress$ or immunomodulat$) ADJ2 (agent$1 or treatment$1 or
   drug$1 or therap$)
2. Antimetabolite$ or Azathioprine or Methotrexate or "Mycophenolic Acid" or
   Alkylating Agent$ or Cyclophosphamide or Chlorambucil or Cyclosporine or
   Tacrolimus or Sirolimus or Rapamycin or amethopterin OR "Mycophenolate
   Mofetil" OR cytophsphane OR FK-506 OR fujimycin OR Imuran OR Azasan
   OR rheumatrex OR cellceplt OR trexall OR myfortic OR cytoxan OR endoxan
   OR cytoxan OR neosar OR procytox OR revimmune OR chlorambucil or
   leukeran or "calcineurin inhibitor$" or gengraf or neoral or sandimmune or
3. prograf or advagraf or protopic or rapamune
4. 1 AND (2 OR 3)

Results = 85

Explanation of Syntax Used:
- the dollar sign ($) finds all variations of word endings (i.e., comput$ finds computer, computing, etc.)
- the number sign (#) finds words that may appear with or without an extra letter (i.e., computer# finds computer or computers)
- the Adjacency Operator (ADJ) searches for 2 or more words that appear within a specified number of words (or fewer) of each other and in any order (i.e., "tax ADJ5 reform" would find instances of "tax reform" as well as "reform of income tax")
BIOSIS Previews
Timespan: 1926-present (updated 2012-07-13)

SEARCH STRATEGY

Topic=(Uveitis or "Ocular inflammat*" or "Intraocular inflammat*")
AND
Topic=((Immunosuppress* or immunomodulat*) NEAR/1 (Agent& or Treatment$ or drug$ or
therap*))
AND
Topic=(Antimetabolite$ or Azathioprine or Methotrexate or "Mycophenolic Acid" or
Alkylating Agent$ or Cyclophosphamide or Chlorambucil or Cyclosporine or Tacrolimus or
Sirolimus or Rapamycin or amethopterin OR "Mycophenolate Mofetil" OR cytophosphane
OR FK-506 OR fujimycin OR Imuran OR Azasan OR rheumatrex OR cellcept OR trexall OR
myfortic OR cytoxan OR endoxan OR cytoxan OR neosar OR procytox OR revimmune OR
chlorambucil or leukeran or "calcineurin inhibitor$" or gengraf or neoral or sandimmune or
prograf or advagraf or protopic or rapamune)
AND
AND Concept Codes=(Pathology - Inflammation "and" inflammatory disease OR Pathology -
Inflammation "and" inflammatory disease)

Results = 112

Explanation of Syntax Used:
- the asterisk sign (*) finds all variations of word endings (i.e, comput* finds computer,
computing, etc.)
- the dollar sign ($) finds words that may appear with or without an extra letter (ie, computer$
finds computer or computers)
- the Near Operator (N) searches for 2 or more words that appear within a specified number of
words (or fewer) of each other and in any order (ie, "tax NS reform" would find instances of
"tax reform" as well as "reform of income tax")
Web of Science
Timespan: 1898-present (updated 2012-07-13)

includes Citation Databases:
- Science Citation Index Expanded (SCI-EXPANDED) --1945-present
- Social Sciences Citation Index (SSCI) --1898-present
- Arts & Humanities Citation Index (A&HCI) --1975-present
- Conference Proceedings Citation Index- Science (CPCI-S) --1990-present
- Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990-present

SEARCH STRATEGY

Topic=(Uveitis or "Ocular inflammat*" or "Intraocular inflammat*")
AND
Topic=((Immunosuppress* or immunomodulat*) NEAR/1 (Agent& or Treatment$ or drug$ or therap*))
AND
Topic=(Antimetabolite$ or Azathioprine or Methotrexate or "Mycophenolic Acid" or Alkylating Agent$ or Cyclophosphamide or Chlorambucil or Cyclosporine or Tacrolimus or Sirolimus or Rapamycin or amethopterin OR "Mycophenolate Mofetil" OR cytophosphane OR FK-506 OR fujimycin OR Imuran OR Azasan OR rheumatrex OR cellcept OR trexa ll OR myfortic OR cytoxan OR endoxan OR cytoxan OR neosar OR procytox OR revimmune OR chlorambucil or leukeran or "calcineurin inhibitor$" or gengraf or neoral or sandimmune or prograf or advagraf or protopic or rapamune)

Results = 275

Explanation of Syntax Used:
- the asterisk sign (*) finds all variations of word endings (i.e, comput* finds computer, computing, etc.)
- the dollar sign ($) finds words that may appear with or without an extra letter (i.e, computer$ finds computer or computers)
- the Near Operator (N) searches for 2 or more words that appear within a specified number of words (or fewer) of each other and in any order (i.e, "tax N5 reform" would find instances of "tax reform" as well as "reform of income tax")
Appendix D: Study Eligibility Criteria

Level 1 Screening:
1. Does the study look at non-infectious idiopathic uveitis in humans?
2. Is it a primary study?
3. Does the study look at immunosuppressive treatments: antimitabolites, alkylating agents, T-lymphocytes inhibitors?
4. Was the study conducted in North America, Western Europe, Hong Kong, Japan, New Zealand, Australia, and Singapore?
*Answer to all questions must be a yes in order to be included for level 2 screening.

Level 2 Screening:
1. Does the study look at non-infectious idiopathic uveitis (keep studies that have 50% or more of patients with non-infectious idiopathic uveitis or Juvenile rheumatoid arthritis associated with uveitis)? Studies with 50% or more patients with these diseases were excluded from study:
   - Behcets disease
   - Vogt-Koyanagi-Harada
   - HLA B27
   - Serpiginous choroiditis
   - Cystoid macular oedema
   - Atopic keratoconjunctivitis
   - Vasculitis
   - ocular cicatrical Pemphiod
   - Wegener’s granulomatosis
   - Sclerosis
   - Sarcoidosis
2. Location of disease either posterior or intermediate or panuvitis. If 50 % or more patients have anterior uveitis, the study is excluded.
3. Is it a primary study?
4. More than 5 patients?
5. The study population had oral treatment given
6. Does the study look at immunosuppressive treatments: antimitabolites, alkylating agents, T-lymphocytes inhibitors?
7. Does the study report any one of these outcomes: Visual acuity, inflammation grade, relapse rate, corticosteroid sparing rate and/or adverse events?
8. Was the study conducted in North America, Western Europe, Hong Kong, Japan, New Zealand, Australia, and Singapore?
9. Is the study in English?
Appendix E: Data Extraction Form

Reviewer's Initial:

(Please check the second page if terminology is unclear)

<table>
<thead>
<tr>
<th>Study Identification</th>
<th>Method</th>
<th>Participant Characteristics</th>
<th>Baseline Characteristics (Before Treatment)</th>
<th>Treatment</th>
<th>Outcomes (After treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citation (author, year):</td>
<td>Study objective:</td>
<td>N (Full) = Ni (idiopathic uveitis) =</td>
<td>Location of Uveitis:</td>
<td>Treatment given:</td>
<td>Pre and Post Visual Acuity</td>
</tr>
<tr>
<td></td>
<td>Study design:</td>
<td>Mean age:</td>
<td>Cause of Uveitis:</td>
<td>Dosage (per week):</td>
<td>(given either in % or the number of patients)</td>
</tr>
<tr>
<td></td>
<td>Site(s):</td>
<td>% Female:</td>
<td>Type of Uveitis:</td>
<td>Length of time:</td>
<td>Reduction in Severity</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria:</td>
<td>Race/ethnicity (and %):</td>
<td>Severity of Uveitis:</td>
<td>Concurrent Treatment:</td>
<td>Via:</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria:</td>
<td>Geographic location (of study):</td>
<td>Measured via inflammation grade</td>
<td>Dosage (per week):</td>
<td>Visual Acuity:</td>
</tr>
<tr>
<td></td>
<td>Data collection technique:</td>
<td>Mean Follow Up (months):</td>
<td>Or/And</td>
<td>Length of time:</td>
<td>Or and</td>
</tr>
<tr>
<td></td>
<td>Date(s) of data collection:</td>
<td>Lost to follow up:</td>
<td>Visual Acuity (LogMAR):</td>
<td></td>
<td>Inflammation grade:</td>
</tr>
</tbody>
</table>

N (Full) = total number of patients considered. Ni = Total number of patients with idiopathic uveitis
### Appendix F: Downs and Black Checklist for Study Quality

**Checklist for measuring study quality**

**Reporting**

1. *Is the hypothesis/aim/objective of the study clearly described?*

<table>
<thead>
<tr>
<th>yes</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>0</td>
</tr>
</tbody>
</table>

2. *Are the main outcomes to be measured clearly described in the Introduction or Methods section?*

   If the main outcomes are first mentioned in the Results section, the question should be answered no.

<table>
<thead>
<tr>
<th>yes</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>0</td>
</tr>
</tbody>
</table>

3. *Are the characteristics of the patients included in the study clearly described?*

   In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.

<table>
<thead>
<tr>
<th>yes</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>0</td>
</tr>
</tbody>
</table>

4. *Are the interventions of interest clearly described?*

   Treatments and placebo (where relevant) that are to be compared should be clearly described.

<table>
<thead>
<tr>
<th>yes</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>partially</td>
<td>1</td>
</tr>
<tr>
<td>no</td>
<td>0</td>
</tr>
</tbody>
</table>

5. *Are the distributions of principal confounders in each group of subjects to be compared clearly described?*

   A list of principal confounders is provided.

<table>
<thead>
<tr>
<th>yes</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>0</td>
</tr>
</tbody>
</table>

6. *Are the main findings of the study clearly described?*

   Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below.)

<table>
<thead>
<tr>
<th>yes</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>0</td>
</tr>
</tbody>
</table>

7. *Does the study provide estimates of the random variability in the data for the main outcomes?*

   In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.

<table>
<thead>
<tr>
<th>yes</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>0</td>
</tr>
</tbody>
</table>

8. *Have all important adverse events that may be a consequence of the intervention been reported?*

   This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided.)

<table>
<thead>
<tr>
<th>yes</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>0</td>
</tr>
</tbody>
</table>

9. *Have the characteristics of patients lost to follow-up been described?*

   This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

<table>
<thead>
<tr>
<th>yes</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>0</td>
</tr>
</tbody>
</table>
10. *Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>no</td>
<td>0</td>
</tr>
</tbody>
</table>

**External validity**

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalized to the population from which the study subjects were derived.

11. *Were the subjects asked to participate in the study representative of the entire population from which they were recruited?*

The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>no</td>
<td>0</td>
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</table>

12. *Were those subjects who were prepared to participate representative of the entire population from which they were recruited?*

The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

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13. *Were the stay, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?*

For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.

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**Internal validity — bias**

14. *Was an attempt made to blind study subjects to the intervention they have received?*

For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

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15. *Was an attempt made to blind those measuring the main outcomes of the intervention?*

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16. *If any of the results of the study were based on “data dredging”, was this made clear?*

Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.

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17. *In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?*

Where follow-up was the same for all study
patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.

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18. **Were the statistical tests used to assess the main outcomes appropriate?**

The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.

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19. **Was compliance with the intervention/s reliable?**

Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.

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20. **Were the main outcome measures used accurate (valid and reliable)?**

For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.

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21. **Internal validity — confounding (selection bias)**

21. **Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?**

For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.

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</table>

22. **Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?**

For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

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23. **Were study subjects randomized to intervention groups?**

Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.

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</table>
24. Was the randomized intervention assignment concealed from both patients and health care stay until recruitment was complete and irrevocable?
All non-randomized studies should be answered no. If assignment was concealed from patients but not from stay, it should be answered no.

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26. Were losses of patients to follow-up taken into account?
If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.

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Power

27. Did the study have sufficient power to detect a clinically important event where the probability value for a difference being due to chance is less than 5%?
Sample sizes have been calculated to detect a difference of x% and y%.

<table>
<thead>
<tr>
<th>Size of smallest intervention group</th>
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<tbody>
<tr>
<td>A $&lt;n_1$</td>
<td>0</td>
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<tr>
<td>B $n_1-n_2$</td>
<td>1</td>
</tr>
<tr>
<td>C $n_2-n_3$</td>
<td>2</td>
</tr>
<tr>
<td>D $n_3-n_4$</td>
<td>3</td>
</tr>
<tr>
<td>E $n_4-n_5$</td>
<td>4</td>
</tr>
<tr>
<td>F $n +$</td>
<td>5</td>
</tr>
</tbody>
</table>
Curriculum Vitae

Name: Hargurinder Singh

Post-secondary

Western University
London, Canada
2012-2015 M.Sc.

University of Toronto
Toronto, Canada
2007-2011 B.Sc.

Honours and Awards:

Western Graduate Research Scholarship
Western University
2012-2014

Awarded 1st prize in the poster category
10th Annual Graduate Student Research Day at Women’s College 2011

Presentations

CSEB 2014: Poster Presentation: Title: Effectiveness of immunosuppressive treatments on idiopathic non-infectious uveitis: A Systematic Review and Meta-analysis.

London Health Research day 2013: Poster Presentation. Title: Effectiveness of immunosuppressive treatments on idiopathic non-infectious uveitis: A Systematic Review and Meta-analysis.


10th Annual Graduate Student Research Day – Women’s College: Poster Presentation. Title: Puberty in females enhances the risk of an outcome of multiple sclerosis in children and the development of central nervous system autoimmunity in mice.