Adverse Effects and Pharmacokinetic Characteristics of High-Dose Glucocorticoid Treatment in Children with Rheumatic Diseases

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Physiology and Pharmacology
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Abstract

This integrated-article thesis explores the impact of long-term glucocorticoid (GC) therapy on children with RD. Long-term GC treatment is potentially associated with severe adverse drug reactions (ADRs). Our scoping review summarizes the current evidence health-related quality of life (HRQOL) impacts of this treatment on children with RD. We describe the frequency of ADRs related to long-term GC treatment in a convenience sample of pediatric RD patients on long-term prednisone therapy and evaluate clinical characteristics that may be associated with risk for of GC-related ADRs. Lastly, we present a pilot study to evaluate the feasibility of monitoring GC PK in children with RD in a prospective cohort with RD. We focus on prednisone, in particular, which is a synthetic GC used in high doses to manage moderate to severe inflammation in children with rheumatic diseases (RD). Our preliminary work demonstrates that patient factors such as baseline body-mass-index and PK variability may be associated with GC-related ADRs, which supports the need to refine our understanding of the dose-response relationship in GC treatment.

Keywords
Toxicity, Adverse Effects, Glucocorticoids, Prednisone, Children, Rheumatic Diseases

Summary for Lay Audience

Prednisone is a medication that is a synthetic glucocorticoid (GC) which has been associated with severe side effects, especially in children. Side effects may include weight gain, depression and anxiety, cataracts, diabetes, high blood pressure, weak bones, and growth problems. This work summarizes the burden of prednisone side effects in children with rheumatic diseases (RDs). First, we examined the impact of treatment with prednisone on health-related quality of life (HRQOL), by critically evaluating the current literature on this topic. We explored patient and disease related risk factors for children with RD treated with high-dose prednisone to develop side effects using a chart review of patients seen at a single
academic pediatric rheumatology center. This thesis also explored the variability between the concentrations of GC in the blood after taking standardized weight-based doses, and the influence on drug concentration to the development of side effects. We conclude that patient factors such as concentrations of prednisolone in the blood and baseline body-mass-index (BMI) may contribute to a patient’s likelihood of developing side effects such as weight gain in children with RD. This work adds to the body of evidence that personalizing and adjusting doses of prednisone based on patient-specific factors (like blood concentrations) may reduce the risk of developing severe side effects to this treatment.
Co-Authorship Statement

Dr. Roberta Berard, Dr. Jonathan Park and Dr. Erkan Demirkaya have graciously screened their patients for study participation and provided clinical and methodological expertise to inform the studies published in this thesis.

Dr. Barbara Murray helped review articles for the Scoping Review.

Dr. Michael Miller and Dr. Craig Nathanson contributed to the statistical analysis of the retrospective chart review and the scoping review respectively.

Dr. Rommel Tirona provided laboratory supervision, reviewed experimental protocols and supported my interpretation of the laboratory data.

Dr. Michael Rieder provided oversight of the various activities summarized by the current thesis.
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I would like to acknowledge the support of Nancy Friedrich, Dr. Barbara Murray, and Sarah Wells, who have provided me with assistance with sample collection and questionnaires. Ms. Friedrich has provided support for the laboratory work published in this thesis. Darren Hamilton has kindly assisted with the literature search for the scoping review.

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I would like to thank the Clinical Investigator Program for providing me with protected research time to allow these study procedures to be completed, and to the Children’s Health Research Institute, for the Translational Research Grant, for financially supporting this study.

I am profoundly grateful for the support provided by my husband, Dr. Erik van Oosten, for his unwavering support, integrity, and wise perspective that has nurtured my curiosity and intellectual authenticity over the years. Thank you for making this scholarly work possible. To my boys, Maximilian and Theodore, you inspire me to love and to learn, and above all, to keep my mind open to all possibilities. To my mother, for your unconditional love, and to my siblings, Rachel and Ernest, my cheerleaders - especially in times of failure – thank you.

I would like to acknowledge all the patients and families who participated in this study. They donated their blood, time, and energy to this project, with the aim of making GC-treatment safer for children with RD in the future. I hope my work will articulate the issues that must be improved to lower the burden of GC-treatment on patient outcomes.

This thesis is dedicated to the memory of my father, Allan, to whom I owe my thirst for knowledge and my love for the field of medicine. Thank you for teaching me the value of finding opportunity in failure, and the joy that comes with an open mind.
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List of abbreviations:

ADR- Adverse drug reaction

BMI – Body-mass-index

cSLE- Childhood systemic lupus erythematosus

CTCAE – Common Terminology Criteria for Adverse Events

DMARD- Disease modifying agent for rheumatic disease

GC- Glucocorticoid

GTI- Glucocorticoid Toxicity Index

HRQOL- health-related quality of life

JDM- juvenile dermatomyositis

JIA- juvenile idiopathic arthritis

NSAID- non-steroidal anti-inflammatory drug

PedsQL- Pediatric Quality of Life Inventory – core generic module

PedsQL-RM – Pediatric Quality of Life Inventory – rheumatology module

pGTI- pediatric Glucocorticoid Toxicity Index

PGA- Physical Global Assessment (of disease activity)

PK – Pharmacokinetics

QUEST – Quality of Life Evaluation on Steroid Treatment

TDM – Therapeutic Drug Monitoring
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Chapter 1

1 Introduction

Prednisone is a synthetic glucocorticoid (GC) used to treat moderate to severe presentations of rheumatic diseases (RD) in children. Pediatric RDs include juvenile idiopathic arthritis (JIA), childhood systemic lupus erythematosus (cSLE), juvenile dermatomyositis (JDM), and systemic vasculitis (SV) such as c-ANCA vasculitis, and Takayasu’s arteritis. The estimated prevalence of childhood RDs is relatively rare, ranging from 1 in 1,000 for JIA, \(^1\) 1 in 100,000 in cSLE, \(^2,3\) and to 1 in 1,000,000 for JDM and systemic vasculitis. \(^4,5\) Despite the introduction of biologic therapy, prednisone is still used commonly to treat severe systemic inflammation. Treatment with prednisone is associated with long-term adverse drug reactions (ADRs) - unintended and undesired effects of medications when taken at the as prescribed. \(^6\) Collectively, children with chronic RD who require prednisone can be at risk of treatment-related complications due to long duration of treatment, and high doses required to achieve disease remission. \(^7-9\)

This integrated article thesis examines the burden of long-term GC treatment on children with RD. The first objective of this thesis is to review the current literature and methodological approaches in studying the impact of GC-treatment on health-related quality of life (HRQOL) in childhood RD. The second objective for this thesis is to explore patient characteristics that represent higher risk for GC-related ADRs. The third objective is to explore potential mechanistic causes of GC-toxicity, such as the pharmacokinetic (PK) profiles of prednisolone and the possible impacts on treatment response and toxicity. Each chapter is currently in manuscript, with the eventual goal of submitting to a peer-reviewed journal.

I hypothesize that GC-toxicity has a negative impact on HRQOL in children with RD, and that despite standardized weight-based doses of prednisone, risk of side effects may be related to variability in concentrations of GC medication in the blood. This thesis further explores the potential role of GC-PKs in identifying patients who are at high risk of developing ADRs.
**Prednisone metabolism and mechanisms of ADRs**

Prednisone is a prodrug that is metabolized to active prednisolone in the liver by the type 1 11β-hydroxysteroid-dehydrogenase (11βHSD1) enzyme. While prednisolone has affinity with the mineralocorticoid receptor, this interaction is prevented by the expression of 11βHSD type 2 (11βHSD2) enzyme that inactivates 11-hydroxy steroids back to their prodrug form; this is especially true in tissues such as the kidney. Due to their highly lipophilic structure, GCs pass readily through membranes. The ubiquity of GC receptors (GR) throughout the body contributes to the wide array of potential side effects in various organ systems. The GR receptor is encoded by the NR3C1 gene, and various polymorphisms have been implicated in interindividual variation in the sensitivity to the drug. There are at least 8 translational isoforms, which account for additional GR diversity, which differ in their ability to regulate gene expression.

GCs bind to cytosolic GR and subsequently translocate to the nucleus where they are thought to mitigate repression of inflammation by interfering with transcription factors required to maintain cellular inflammation pathways. This mechanism is called transrepression. ADRs which are unintended effects experienced at usual treatment doses, occur via a mechanism where the direct binding to the glucocorticoid response element (GRE) is thought to lead to the activation of genes that lead to the development of undesired responses associated with GC-therapy – this is known as transactivation. While endogenous GCs such as cortisol are essential to life, supra-physiologic doses initiate a different set of effects on organ systems. As an example, instead of an immunomodulatory role, high-dose GCs demonstrate an immunosuppressive role. With prednisolone being five times more potent than cortisol, the immunosuppressive effects are clearly demonstrated. GCs bind to cytosolic GR and subsequently translocate to the nucleus where they are thought to mitigate repression of inflammation by interfering with transcription factors required to maintain cellular inflammation pathways. This mechanism is called transrepression.

While endogenous GCs such as cortisol are essential to basic homeostatic functions such as immunomodulation and glucose homeostasis, supra-physiologic doses initiate a
different set of effects such as visceral obesity, muscle myopathy, hypertension, and insulin resistance.\textsuperscript{11,14} At high doses, GCs demonstrate an immunosuppressive role instead of an immunomodulatory role.\textsuperscript{15} The severity of ADRs is dose-dependent, and therefore, many children with RD eventually develop ADRs on long-term prednisone therapy. Specific ADR mechanisms are tissue-specific due to the range of GR isoforms, and the expression of enzymes that would activate and deactivate GCs.\textsuperscript{16} Prednisolone is converted in local tissues to inactive prednisone by 11-\textbeta HSD2, which subsequently leads to the irreversible 5\alpha- or 5\beta-reduction to tetra-prednisone and other inactive metabolites.\textsuperscript{17} These metabolites are cleared renally.

In the plasma, both prednisone and prednisolone are protein-bound, binding to albumin, as well as corticosteroid-binding globulin.\textsuperscript{18} At physiologic doses, much of the endogenous steroid is protein-bound. However, at high doses, most of the prednisolone is in its free unbound form, as protein binding sites are saturated.\textsuperscript{18} This excessive exposure of free-unbound prednisolone is thought to be the reason for increased exposure to non-target tissues, and the eventual to GC-related ADRs, as well as immunosuppressive effects.

Aside from the dose and duration of GC treatment, children and adolescents with RD are at significant risk for GC-related ADRs as they are in periods of active growth. As GCs mediate direct effects on the bone, long-term exposure to high-doses of GCs affects bone mineralization and lead to growth suppression.\textsuperscript{19} Moreover, children with RD may have disease involvement that affects renal and hepatic function, which also influences the risk of GC-related ADRs. Due to these risk factors, children with RD may be particularly vulnerable to the effects of GC-related ADRs related to growth and development.

To study the concentrations of medication in the blood over time, PK studies are valuable.\textsuperscript{18,20,21} Few have been performed in children in a clinical context as they require several blood samples that are taken over a period of a few hours, and sometimes, over a 24 hour period.\textsuperscript{22,23} PK studies provide a direct measure of the concentrations of prednisolone, the biologically active metabolite of prednisone, in the blood. In adults, the
concentration of unbound prednisolone has been correlated with the subsequent effects on GC treatment response and tendency to develop ADRs.

There are several patient risk factors that can affect prednisolone PK. Plasma clearance of prednisolone may be related to GC-related ADRs. For example, severe renal disease can delay clearance of prednisolone from the blood. This has been previously associated with increased side effects of weight gain and fluid retention in adult renal transplant patients. Impaired hepatic function can also decrease the rates of conversion from prednisone to prednisolone, which may actually decrease the peak concentrations of prednisolone in the blood. Lower levels of albumin may also affect the relative amount of free, unbound prednisolone, which is potentially associated with greater frequency of side effects. Higher body mass index (BMI) has been associated with changes in clearance rates another GC, methylprednisolone, although the relationship is not well understood. These clinical features of patients have yet to be evaluated as risk factors for the development of GC-related ADRs.

Measuring GC-ADRs

For children with childhood RD, the burden of long-term exposure to GC persists to adulthood. Often, patients with cSLE require GC therapy for years after their initial diagnosis, leading to damage accrual from both GC-treatment and disease activity. In a recent study on adults with cSLE, almost 80% of patients still required GC treatment, with most patients reporting some degree of disease-induced and treatment-related damage after 5 years of diagnosis. The pediatric Glucocorticoid Toxicity Index (pGTI) was published in October 2022, and prior to that there was no standardized method used to report GC-related ADR in children, other than the Common Terminology of Criteria for Adverse Effects, although they were rarely used in the documentation of GC-related AEs outside of clinical trials. Long-term treatment with GCs is associated with long-term toxicity, which may exacerbate disease related complications. Children with cSLE, as an example, are known to have lower bone mineral density, due to the ongoing effects of inflammation on nutritional status exacerbated by GCs. Despite the side effects, patients are willing to tolerate GC if they perceive that treatment is effective. Therefore, for
many patients, the beneficial properties of GCs such as the accessibility, ease of administration, and effectiveness of GCs make them a practical choice to include in the treatment of inflammation in children with RD.

1.1 Impact of long-term GC-toxicity on health-related quality of life outcomes

The first objective of this thesis was to critically evaluate the literature supporting the burden imposed by long-term GC therapy on HRQOL in children with RD. While this has been a longstanding area of clinical interest for pediatric rheumatologists, much of the work has been difficult to summarize due to the use of different outcome measures and definitions of HRQOL, and inadequate power of studies to evaluate relationship of GC-treatment and HRQOL, and lack of instruments that can differentiate the impact of ADRs from effects of disease activity. In addition, the study of HRQOL due to GC is difficult in this population, as children are often taking more than one medication, and therefore it is difficult to isolate the effect specific to GC in the context of polypharmacy.

The use of standardized reporting tools for GC-related HRQOL measures have been lacking in this field of study. This is a significant gap given that children with RD are at higher risk for GC-related ADR. The tool that had been used previously was the Common Terminology for Common Adverse Effects, which was developed for clinical trials in adult oncology, and subsequently adapted to pediatric oncology population. However, this is not routinely used in clinical practice, or in research studies in the pediatric rheumatology population.

For the measurement of HRQOL in children with RD, there are several validated tools that are used in RD. No specific GC-HRQOL tool has been validated for children with RD. However, there is one such tool that has been developed for children with acute lymphoblastic leukemia, the Quality-of-Life Evaluation in patients receiving Steroids (QUEST) tool. Some of the strengths of this tool include the inclusion of several domains that impact child and adolescent HRQOL that may be directly influenced by their GC-related ADRs. For instance, the tool measures the impact of changes in physical
appearance and mood on HRQOL in children and adolescents. Despite these relative strengths, the QUEST tool has not been validated in children with RD and is not routinely used in clinical care as an outcome tool.

Studies on the impacts of ADRs on HRQOL in children with chronic RD should ideally account for the effects of disease activity. This is particularly important in children with disease manifestations that can overlap with the GC-related ADRs. For instance, in cSLE, neuropsychiatric changes can result in psychosis, mood disturbance, and behaviour changes. These can demonstrate some overlap with GC-related effects.

I hypothesize that this therapy is associated with significant ADRs that directly impact HRQOL, but that this burden is likely only partially captured, due to a lack of consensus in standardized documentation on GC-related ADRs, and methods to account for disease related activity on HRQOL scores.

### 1.2 Glucocorticoid related adverse effects in children with rheumatic disease

As the second objective of this thesis, we sought to evaluate clinical variables that are known to alter prednisolone PK as risk factors for GC-toxicity in children with RD. While the risk for GC-toxicity is proportional to dose and duration of GC-treatment, other variables that affect pharmacokinetic parameters, such as age, biological sex, and underlying disease may also affect the risk of developing these toxicities. It is difficult to accurately estimate the prevalence of ADRs across different studies without standardized reporting criteria and measurement tools for GC-toxicity.

Current evidence suggests that children are at a higher risk of experiencing side effects, perhaps due to being in an active phase of growth and development. Long-term GC use can lead to a higher risk for vertebral fractures and osteoporosis in children, with a prevalence of 6% for incident vertebral fractures, which is lower than observed in adults. For many patients who have significant changes to baseline BMI on long-term GC therapy, 25% of patients do not return to baseline z-scores at 18 months even after discontinuing therapy. A systematic review of the literature estimated that around 20%
of children on long-term prednisone treatment developed GC-related weight gain.\textsuperscript{44} Around 59\% were estimated to have hypothalamic-pituitary-adrenal axis suppression, although this is often difficult to change clinical management due to need for ongoing use of GCs due to underlying disease activity. Growth retardation was noted to affect 18\% of patients, but other side effect such as cataracts and hypertension occurred in just above 5\%.\textsuperscript{44} Glucose intolerance, central obesity, skin thinning and acne were common and bothersome, therefore suggesting that interventions to prevent them may be beneficial for patients.\textsuperscript{44} Central nervous system effects such as anxiety and depression are also common with GC-treatment.

The burden of long-term GC treatment is a growing area of clinical concern. In the past 5 years, clinicians have collaborated across specialties to create the pGTI, in order to better document the burden of GC-ADRs in children.\textsuperscript{28} This reporting tool defines a standardized list of GC-specific ADRs and classifies severity. These criteria are in line with the framework of the CTCAE that was initially used in the study of ADRs related to cancer treatment, and now applied conceptually to other areas of medicine.\textsuperscript{29} While the pGTI criteria were published in 2022, they have yet to be implemented clinically or have established use in clinical trials. Nevertheless, this represents an important tool in the study of GC-toxicity, to tease out the role of GC-related ADRs in the context of polypharmacy. My thesis hypothesizes that the frequency of ADRs in children with RD is likely higher than those reported in other paediatric populations.

1.3 Prednisolone Pharmacokinetics in children in children with rheumatic disease

The third objective of this thesis is to study the feasibility of studying PK in children, and to explore the potential value of PK as a tool to identify a mechanism of risk related to GC-toxicity. In children, disease severity, renal function, hepatic function, and hypoalbuminemia, affect the bioavailability of prednisolone.\textsuperscript{18} Age affects PK parameters of prednisolone, as younger patients are noted to have faster clearance rates, shorter half-lives, and more efficient drug elimination, a trend that is maintained when comparing PK parameters in children, as compared to adults.\textsuperscript{45} The effect of biological sex and PK is also not clearly understood, as many of the PK experiments in children were unable to
study this question due to inadequately powered study samples to explore any potential mechanisms for different sex-based response.\textsuperscript{46} Disease states that affect renal clearance, or result in decreased albumin levels have been found to be associated with a higher risk of developing Cushingoid side effects in patients with kidney transplants.\textsuperscript{24} In addition, patients with severe chronic liver disease have less bioavailability of prednisolone likely due to impairments in metabolizing prednisone to prednisolone.\textsuperscript{26} PK data on children is limited due to lack of acceptability of procedures required to obtain blood to patients and parents.\textsuperscript{47} There is little understanding of how this variation in PK translates to ADR, and a lack of prospectively collected data to support that PK may be a useful tool to identify risk for GC-toxicity in children.

I hypothesize that PK studies in children on GCs are feasible in children with RD, and that variability in PKs may reflects the different responses children develop while on treatment including risk of developing ADRs.

The goal of this thesis is to add to our current understanding of the burden of GC toxicity in children with RD. For decades, GCs have been used in the treatment of childhood RD, and yet, little is known about the effects on HRQOL from long-term GC use and the potential for PK as a tool to guide drug dosing to mitigate the risk of toxicity while preserving clinical effectiveness. Measurement tools to study the burden of GC-toxicity in this population have only been recently developed. This work adds to our understanding of the burden of GC-toxicity in for children with RD and proposes potential PK methods to evaluate the risk of ADRs. In doing so, the work in this thesis forms the foundation for future protocols of PK monitoring of prednisolone in children and identifies future areas to improve PK protocols in this population, to improve tolerability and generalizability of therapeutic drug monitoring as a potential strategy for GC-dosing stewardship and minimizing treatment-related toxicity.
Chapter 2

2 The impact of glucocorticoid treatment on health-related quality of life in children with rheumatic diseases: A Scoping Review

Long-term GC therapy is used to treat moderate to severe presentations of childhood RDs, which include JIA, cSLE, JDM, and SV. The prevalence of these conditions is estimated to be 1:1000 in JIA, \(^1\) 1 in 100,000 in cSLE, \(^2\) 1:1,000,000 in JDM, \(^4\) 1:1,000,000 in SV. \(^5\) While biologic therapy has dramatically improved treatment outcomes for some conditions such as JIA, GCs including prednisone and methylprednisolone remain a cornerstone in the management of cSLE and JDM. \(^19\),\(^48\),\(^49\) Medium-dose prednisone is defined as 5 mg to <30 mg per day, or \(\geq 0.2\) to <1 mg/kg/day) and high dose is defined as 30 mg per day, or \((\geq 1\) mg/kg/day). \(^60\) While GC-treatment effectively reduces inflammation in these conditions, long-term exposure to GC therapy has been associated with organ damage and poor health outcomes, which affect patients with childhood-onset disease disproportionately, due to longer duration of disease and treatments. \(^7\),\(^30\)

HRQOL is a multidimensional construct that describes the effect of a disease and its treatment on an individual’s perceptions of their health across several domains, including physical, emotional, mental, and social functioning. \(^50\) In the pediatric population, parent proxy reporting is often required especially for younger children who may not fully understand evaluated constructs. \(^35\),\(^51\),\(^52\) In general, child and proxy agreement has been found to be acceptable but the factors that may affect this remain poorly understood, suggesting that such tools should be used with the knowledge that there may be a discordance between parent and child reports. \(^53\) The Child Health Questionnaire (CHQ) was one of the first HRQOL tools studied in general pediatric populations, \(^54\) and since then, other HRQOL tools that were developed include: the Pediatric Quality of Life Inventory (PedsQL), \(^38\) the German generic quality of life instrument (KINDL), \(^55\) and the TNO-AZL Children’s Quality of Life Questionnaire (TACQOL), \(^56\) the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)\(^57\) and the Quality of My Life (QoML) questionnaire. \(^34\) More recently, disease-specific quality of life measures for rheumatology-specific HRQOL measures including the Juvenile Arthritis Quality of Life
module, and PedsQL-Rheumatology Module have been developed well. The long-term ADRs associated with GC-use on HRQOL in children with RD has been an important clinical treatment outcome for clinicians, patients and their families. The actual impact of GC-related ADRs on HRQOL has yet to be well described, although many clinicians are highly concerned about the intermediate and long-term impacts on patient outcomes.

To derive a sense of best practices in the study of GC-related impact on HRQOL childhood RD, we conducted a scoping review to critically appraise all articles that looked at the effect of GC-treatment on children with RD. The study in this area is complex, as children and adolescents may experience a range of symptoms related to systemic inflammatory diseases, which may affect HRQOL measurements in this population. In addition, this population may be treated with concurrent medications, which makes it challenging to isolate HRQOL specifics to GC-related ADR without appropriate controls. Given that clinicians and patients have been concerned about GC-related ADRs, we wanted to summarize what is the current evidence on GC-related ADR impacts, and to understand the key components that need to be addressed to study this question. We also sought to identify if any specific HRQOL tools have been used to study GC-related changes, and if not, how the analysis approach could address any relevant confounders.

The burden of toxicity associated with GC therapy is an active area of clinical and research interest in pediatric rheumatology. The pediatric Glucocorticoid Toxicity Index (GTI) was published in October 2022 to itemize GC-ADRs across multiple organ systems – including weight gain, growth suppression, osteopenia, hypertension, infections, skin changes, mood changes, sleep disturbances, and metabolic ADRs. In children, GC-induced weight toxicity is defined as BMI change > 2 kg/m² of change, or > 5 kg/m² of change compared to prior to starting therapy. Growth suppression in children is defined as decrease in z-score by at least 0.5. Severity is also quantified and there are different weights assigned to GC-related ADRs on the overall global toxicity score. While an important first step in establishing definitions and categorizing degrees of GC-toxicity in a standardized manner, the pGTI is still a clinician-derived toxicity criteria. Therefore, it
is not specifically geared towards the study of HRQOL, which is often patient-reported measure to adequately reflect the patient experience.

In children with chronic RD, HRQOL is negatively impacted by disease activity due to lower function scores and higher pain scores, but to date, has not been evaluated in terms of the effect of treatments themselves. The aim of this scoping review was to summarize the current evidence of the impact of long-term GC treatment on the HRQOL in children with chronic RD. While the burden of GC-related ADRs is well-documented, the specific impact of GC-treatment on HRQOL is not well-summarized in children with RD. By gaining a better understanding of the impact of GC-therapy on HRQOL, this research may help clinicians support patients and families with counseling and interventions to mitigate the impact of ADRs.

Our objective for our scoping review was to summarize the current evidence of the impact of long-term GC treatment on HRQOL in children with RD. I hypothesize that high doses and long-duration of GC treatment place children with RD at risk for lower HRQOL compared to the general population, more than the burden attributable to chronic disease alone.

2.1 Methods:

The scoping review study protocol was based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses extensions for Scoping Reviews (PRISMA-ScR). Inclusion criteria included studies that evaluated HRQOL in participants with childhood systemic RDs (JIA, cSLE, JDM), who were treated with oral or intravenous GCs for more than 2 months. HRQOL could be evaluated into adulthood if treatment with systemic GCs were continued into adulthood.

Electronic database search

A Health Sciences librarian conducted a search in MEDLINE, EMBASE, APA, CINAHL, Web of Science, and Cochrane Central of Controlled Trials from inception to
May 2022, to identify any studies that addressed our study question. The reference lists of all studies were scanned to identify further studies; this identified one additional study. We did not restrict study type or year of publication. The search was deduplicated using a previously published protocol. The full search strategy is included in Appendix 1.

**Study selection and characteristics**

Studies that reported HRQOL in children with JIA, cSLE, and JDM treated with GCs for more than 2 months were included. Studies were included if they reported secondary HRQOL outcome measures that were related to GC treatment. Long-term systemic GC treatment was defined as treatment with prednisone, prednisolone, or methylprednisolone at doses greater or equal to 5 mg per day, or 0.2 mg/kg/day for at least 2 months. We chose the duration of 2 months as this would allow some of the longer-term ADRs to have impacts on HRQOL measurements. We included all study designs including observational studies, randomized control trials and qualitative studies. We excluded any studies that did not report original data, letters to the editor without original data, and non-English or French studies from further review. Two reviewers (RP, BM) independently screened all titles and abstracts. Potential candidates for full text review were also reviewed by both reviewers and inclusion was decided based on discussion regarding the relevance to the research question.

**Data abstraction**

Two reviewers extracted data using standardized Excel forms. Any discrepancies were reconciled by discussion to achieve consensus in consultation with a third party (MJR). Key concepts in the study of HRQOL include parameters of dosing with GC, disease study, HRQOL measure, and the identification and quantification of any confounders related to disease activity, and concurrent medications. ADRs specific to GCs were also considered if they related to a HRQOL domain of measure.

**Critical Appraisal**

All articles were assessed using the QUIPS tool. Studies were graded as low-risk, moderate risk, and high-risk for bias. The exposure was long-term administrations of GC,
and the outcome was HRQOL. The QUIPS tool was selected due to heterogeneity in study type and outcomes reported. Inter-rater agreement was assessed using the Cohen’s Kappa statistic. A K-score <0.00 was considered poor, 0.00-0.20 slight, 0.2-0.4 fair, 0.41-0.6, moderate, 0.61-0.8 substantial, and 0.81-1, almost perfect.

**Synthesis:**

Due to the heterogeneity of the studies that were reviewed, study results pertaining to the effect of corticosteroids on HRQOL were summarized as per the Cochrane criteria:66

- Strong evidence of effect: Most studies of low risk of bias (ROB) showing similar effect (>75% of studies)
- Moderate evidence of effect: Most studies with several moderate to high ROB study showing similar effect, or one study of low ROB.
- Limited evidence of effect: One study reporting the effect.
- Conflicting evidence: Inconsistent findings.
- No evidence: no association with prognostic factor and outcome of interest.

The risk of bias was rated low risk, moderate risk, or high risk for bias, based on the evaluation of possible biases based on the sample collected, study attrition, outcome measurements, confounding factors, and statistical analysis.

**2.2. Results:**

The literature search yielded 362 independent titles, and abstracts, of which 8 met study criteria, and summarized in Figure 1. Reliability between reviewer assessments were considered substantial (K=0.67).
Figure 2-1: Study Selection for Scoping Review

Total Records: 
\( n = 436 \)

Records removed before screening:
Duplicate records removed 
\((n = 75)\)

Records screened 
\((n = 362)\)

Abstracts sought for retrieval 
\((n = 181)\)

Studies assessed for eligibility 
\((n = 21)\)

Studies included in review 
\((n = 8)\)

Records excluded** 
\((n = 214)\)

Abstracts excluded:
Not Quality of Life \((n = 59)\)
Not Glucocorticoid \((n = 64)\)
Treatment < 2 months \((n = 3)\)
Not Rheumatic Disease \((n = 1)\)
Adults only \((n = 18)\)
Full text not available \((n = 15)\)

Reports excluded:
Not Quality of Life \((n = 11)\)
Treatment < 2 months \((n = 1)\)
Not children \((n = 1)\)
Table 2-1: Data charting for HRQOL Impact of GC Treatment

<table>
<thead>
<tr>
<th>First author, year (ref.) Location</th>
<th>Interv</th>
<th>Stud</th>
<th>N/Age</th>
<th>Duratio</th>
<th>GC</th>
<th>Control</th>
<th>QOL measur</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guzman J et al (2014)§ Canada</td>
<td>JIA</td>
<td>Qualit</td>
<td>2-12</td>
<td>Diagnos</td>
<td>No GC No dose</td>
<td>Non e</td>
<td>QoML</td>
<td></td>
<td>Medication side effects are important priorities for youth and parents of youth with JIA, and clinicians. PRs are more concerned about GC side effects than patients. No relationship between GC use and HRQOL was reported.</td>
</tr>
<tr>
<td>Kohut SA et al. (2013)§ Canada</td>
<td>cSLE</td>
<td>Cross</td>
<td>10 and</td>
<td>Cohort</td>
<td>Pred N – 35 /38 (92%). Prednisone dose 0.4 mg/kg ±0.3</td>
<td>Non e</td>
<td>Peds QL or Short Form-36 Health survey</td>
<td>Cohort 1: 10/38, CDI score ≥ 13 Cohort 2: 7/16 (44%) BDI-II score ≥ 10 Prednisone dose correlated with negative self-esteem r=0.37 p=0.04, anhedonia (r=0.39, p=0.02)</td>
<td>Higher GC dose in cohort 1 associated with higher physical depression scores, HRQOL scores lower in self-esteem construct</td>
</tr>
<tr>
<td>Knight A et al. (2017)§ US</td>
<td>CKD and cSLE</td>
<td>Cross - secti</td>
<td>Lupus nephritis n=34</td>
<td>LN: 1.5 years</td>
<td>Pred use (n=20, 59%) and CKD (n=39, 23%), no dose</td>
<td>CKD</td>
<td>PedsQL 4.0</td>
<td>LN higher rates of prednisone use, better attention for CPT-II test, and better executive function in D-KEFS. Current prednisone use was associated with worse CPT-II scores (β=4.48, P=0.01). Current prednisone use associated with decreased HRQOL. (β=7.00; P=0.04)</td>
<td>Current prednisone use is associated with decreased child-reported HRQOL.</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Location</td>
<td>Study Type</td>
<td>Participants</td>
<td>Prednisone Use</td>
<td>Prednisone Dose</td>
<td>HRQOL Measures</td>
<td>Findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>---------------</td>
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<td>----------------</td>
<td>----------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hernandez C et al. (2021)</td>
<td>Columbia</td>
<td>Cross - sectional</td>
<td>N = 40 9-17 years Mean age 14 (SD 2)</td>
<td>NA</td>
<td>Pred use (n=20, 17.6%), dose not given</td>
<td>NA</td>
<td>PQ-LES-Q</td>
<td>Treatment with prednisone associated with higher likelihood of anxiety symptoms (p=0.002). QOL data not reported. Possible association of prednisone and presence of anxious symptoms. No relationship between GC use and HRQOL reported.</td>
<td></td>
</tr>
<tr>
<td>Butbul Aviel, Y. et al (2011)</td>
<td>Canada</td>
<td>Cross - sectional</td>
<td>115 JIA and 40 JDM</td>
<td>Pred use (n=20, 17.6%), dose not given</td>
<td>Pred dose (&lt;5 mg/day or &lt;0.2 mg/kg/day) N=10/51 (obese) and N=13/151 (non-obese)</td>
<td>US population</td>
<td>PedsQL (core scale) PedsQL-RM CHQ</td>
<td>44% - JIA disturbed sleep PedsQL patient and parent core module negatively correlated with HRQOL (r=-0.56, P&lt;0.0001), the CHSQ does not differ between prednisone, DMARDs, and biologics. No clear statistically association with prednisone treatment and sleep scores or HRQOL scores.</td>
<td></td>
</tr>
<tr>
<td>Mina, R et al. (2014)</td>
<td>US</td>
<td>Cross - sectional study</td>
<td>n=202 obese (N=51), non-obese (N=151)</td>
<td>Median age: 15.4 ±3.3 (obese) and 15.8 ±3.1 (non-obese)</td>
<td>Pred use (27 patients / 275 patients), 33 side effects in 50 visits</td>
<td>Non e</td>
<td>PedsQL (core scale) PedsQL-RM CHQ</td>
<td>HRQOL low daily prednisone (&lt; 0.2 mg/kg/day &lt; 5 mg/day) Obesity is associated with decreased HRQOL with lower physical function, and independent of prednisone and MP pulses.</td>
<td></td>
</tr>
<tr>
<td>Chédeville, G. et al. (2022)</td>
<td>Canada</td>
<td>Cross - sectional study</td>
<td>N=249 Oligo JIA108 Poly RF-neg-46 ERA -40 PsJIA-14 sJIA-14 sJIA-14 polyRF pos-7 missing -6</td>
<td>Median age 7.9 (3.4-12.6)</td>
<td>Pred use (27 patients / 275 patients), 33 side effects in 50 visits</td>
<td>Non e</td>
<td>QoML</td>
<td>Prednisone monotherapy or combination therapy had high frequency of ADRs- 66% prednisone in 50 visits, compared to 34.7% NSAID, and 59% for MTX only. Significant difficulty with taking prednisone is reported. QoML was negatively correlated with more ADRs, and with severity of ADRs. Side effects associated with medications have a negative impact on HRQOL. No relationship between GC use and HRQOL reported.</td>
<td></td>
</tr>
<tr>
<td>Riddle R et al. 2006</td>
<td>US</td>
<td>Prospective Cohort study</td>
<td>N=57 pairs</td>
<td>0 years (inception cohort)</td>
<td>MP IV, two doses, 4 months apart</td>
<td>Non e</td>
<td>Peds QL Peds QL-RM</td>
<td>Side effects were most common with IV MP given at first treatment and 4 months later) Greatest improvement of HRQOL from MP, and greatest degree of lowered disease activity</td>
<td></td>
</tr>
</tbody>
</table>
Generic PedsQL and PedsQL RM. Scores had greatest change for MP group, from MP, increased frequency of ADR from MP.

JIA – juvenile idiopathic arthritis
cSLE – childhood systemic lupus erythematosus
CKD- chronic kidney disease
JDM – juvenile idiopathic arthritis
Oligo-JIA – oligoarticular JIA
Poly RF neg. Rheumatoid factor negative polyarticular JIA
ERA – enthesitis-related arthritis
PsJIA – psoriatic arthritis
sJIA – systemic JIA
uJIA – undifferentiated JIA
Poly RF pos. Rheumatoid factor positive polyarticular JIA
NSAID – non-steroidal anti-inflammatory drug
MTX- methotrexate
MP – methylprednisolone
Pred - Prednisone

HRQOL instrument used:

Studies used several validated HRQOL measures. The most commonly used measure was the Pediatric Quality of Life Inventory Generic Core Questionnaire (PedsQL-GC),32,67,70,71,73 and the PedsQL-Rheumatology Module (PedsQL-RM).32,70,71 Studies also used the Quality of My life (QoML)58,72 questionnaire and Child Health Questionnaire (CHQ).71 The PedsQL generic core scales measure physical, school, social and emotional functional domains, and comprise different questionnaires that are adapted to children 2-4 years, 5-7 years, 7-12 years, 13-18 years of age.38 The Child Health Questionnaire comprises of 50 items that have parent and child versions which examines concepts such as physical function, bodily pain-discomfort, limitations in schoolwork and family activities due to physical health, general health perceptions, change in health, limitations in schoolwork and activities due to emotional and behavioral difficulties.54 The QoML questionnaire consists of 2 visual analog scales ranging from 0 (“the worst”) to 100 (“the best”) on double-anchored 100 mm Visual Analog Scale (VAS) for each question stem: one asks “Overall, my life is...” and measures overall QOL; and the other asks “Considering my health, my life is...” and measures HRQOL.34 The Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)57 is a 15-question scale that assesses the attitude regarding general health, well-being, and feelings about life, and is translated to Spanish. For studies evaluating adult patients diagnosed with childhood RD,
the Short-Form 36 was used. A summary of the domains measured by HRQOL are summarized in Figure 3.

**Figure 2-2- HRQOL measurement tools - domains and summary**

Methodologic quality of the studies:

Most studies included small to medium sample sizes. Despite the small sample sizes, most studies were at moderate risk of bias. The appraisal of risk of bias using the QUIPs tool is summarized in Table 2-3. If the study did not adjust their findings to at least one confounder, risk of bias was moderate. If they did not define any confounders and did not adjust for any confounders, the risk of bias was high. There were two major confounders that were considered: the role of disease activity and polypharmacy. Most studies did not adjust for these confounders.
Table 2-2: Assessment of Risk of Bias for GC Exposure as a Prognostic Factor of HRQOL

<table>
<thead>
<tr>
<th>Study</th>
<th>Source of bias</th>
<th>Effect size of GC on HRQOL impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butbul Aviel Y. (2011)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Kohut et al (2013)</td>
<td>Medium</td>
<td></td>
</tr>
<tr>
<td>Knight A. et al (2017)</td>
<td>Low to medium</td>
<td></td>
</tr>
<tr>
<td>Guzman J et al (2021)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Hernandes C. et al (2021)</td>
<td>Medium</td>
<td></td>
</tr>
<tr>
<td>Chédeville G. et al. (2022)</td>
<td>Medium</td>
<td></td>
</tr>
</tbody>
</table>

Factors affecting the impact of GC treatment on HRQOL:

Most studies that we reviewed studied the impact of GC treatment on HRQOL as a secondary outcome. We summarized the effect of HRQOL on patients the side effects due to GCs usage, such as physical appearance, obesity, and sleep issues. We also evaluated domains of HRQOL that were reported as affected by GC-treatment.

Physical appearance and HRQOL

Children and adolescents diagnosed with cSLE who met the criteria for obesity (WHO BMI > 95 %ile) reported significantly lower HRQOL scores as measured by PedsQL core modules, PedsQL RM, and the CHQ. There was no correlation with the dose of
prednisone: the patients with obesity had lower daily prednisone dose compared to their non-obese cohort (mean (mg/kg/day 0.15 ± 0.18 vs 0.32 ±0.48, p-value < 0.0001). Patients with obesity had lower physical function scores. Exploratory analysis reveals that being overweight (BMI 85-95th percentile) did not significantly affect HRQOL scores. Of note, the domain that was spared was the emotional and social domain- where no significant differences were found between obese and non-obese individuals.

**Emotional functioning and HRQOL**

Treatment with prednisone was associated with negative impacts on emotional health, with more anxiety symptoms reported with those receiving GC treatment. While neuropsychiatric symptoms of cSLE can be frequent (up to 42%), patients experience significant emotional dysfunction while on treatment as well. No direct correlation between prednisone and HRQOL scores was noted in this cohort study, but the dose of prednisone was associated with lower self-esteem scores and more anhedonia symptoms based on Childhood Depressive Index (CDI) scores. Over a quarter of patients reported depression scores CDI ≥ 13 (borderline significant depression), and 3 patients had scores meeting the criteria of clinically significant depression. They also present with significant anxiety symptoms, with 60% of patients scoring more than the cut-off of ≥25 anxiety. Patients treated with prednisone had a statistically significantly higher risk of anxiety symptoms, compared to other treatments, including azathioprine, chloroquine, hydroxychloroquine, and mycophenolate.

**Cognitive function and HRQOL**

The effect of high-dose prednisone treatment on cognitive domains of HRQOL has not been clearly established. Mina *et al.* reported lower school functioning for obese individuals compared to non-obese individuals with cSLE, however, obese individuals in this cohort were on lower daily dosing compared to non-obese children. The effect of prednisone treatment in children with cSLE nephritis is associated with improved attention and executive function in some psychometric assessment questionnaires, and lower processing scores as per the CPT-II questionnaire compared to children with other types of chronic kidney disease. However, the duration of disease tended to be longer
in children with CKD in this cohort compared to the lupus nephritis group, with no adjustment to that confounder in the cognitive scores. Lower cognitive function was associated with decreased HRQOL, but the actual impact of high-dose steroid on cognitive function is unclear.\textsuperscript{73}

**Fatigue and Sleep on HRQOL**

Disturbed sleep and fatigue were negatively correlated with HRQOL for patients with JIA and JDM.\textsuperscript{70} Greater fatigue highly correlated with worsened HRQOL as measured by the PedsQL core module in both child and parent proxy reports ($r> 0.70$, $P\leq 0.0001$). The effect of prednisone treatment did not seem to affect Child Sleep Habits Questionnaire (CSHQ) scores in these patients for either the CSHQ scores or the Sleep Self-Report (SSR) scores – although the medication data were not shown.\textsuperscript{70}

**Disease activity and HRQOL**

A single study looked at the intravenous methylprednisolone (MP) treatment of moderate to severe inflammation in JIA over two months compared to other treatment modalities with methotrexate and other DMARDs, and non-steroidal anti-inflammatory drugs (NSAIDs).\textsuperscript{32} Patients had greatest improvements with quality of life, as well as the greatest reduction in disease activity in the MP arm of the study. Patients were willing to tolerate side effects related to GC therapy if there were noticeable improvements in disease activity.

**2.2 Discussion:**

In summary, long-term GC treatment may impact the HRQOL in children with RDs for several reasons, including impacting physical function, physical appearance, self-esteem, and cognitive functions. Pediatric HRQOL scores are more centered on self-esteem and mental functioning. Several observations were particularly interesting – such as the negative impact of obesity on HRQOL in children and adolescents with cSLE. Moreover, obesity and the physical changes associated with disease and treatment are major contributors to the decreased HRQOL scores, but are often recognized as unactionable as clinicians, although they are also concerned about the burden of side effects.
The effects of long-term GC treatment on HRQOL may persist into adulthood. In adults diagnosed with cSLE, changes in their physical appearance due to disease reported lower HRQOL scores in seven out of 8 HRQOL domains. These changes included disease-activity related changes such as alopecia and inflammatory rash. Those with bothersome physical appearance scores reported similar or lower HRQOL scores than patients with high disease activity. This suggests that physical appearance is an important outcome for patients independent of disease activity, and therefore, it may be helpful for clinicians to be aware of toxicities that affect physical appearance as they may be associated with poor HRQOL. Long-term GC treatment was associated with increased disease damage as per Systemic Lupus International Collaborating Clinics (SLICC) criteria. Disease-related damage was more significant 5 years after the diagnosis of cSLE and most patients reported disease and treatment-related damage in their twenties, and damage accrual was associated with disease duration. Treatment with prednisone and other DMARDs were associated with higher disease damage compared to patients on prednisone monotherapy. High disease activity indices, defined as Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) ≥8 and longer disease duration, were associated with lower HRQOL scores across most domains.

This scoping review identified several limitations in the evaluation of GC treatment and effect on HRQOL. First, GCs are often used concurrently with other medications, and therefore the validity of any tool developed for this purpose must account for concurrent medications. Secondly, the damage associated with disease is often difficult to separate from damage associated with long-term treatment with GCs for patients, such as osteoporosis. Third, our review mainly included cross-sectional studies, and thus any correlations would be inadequate to establish any causality of GC and HRQOL.

Current tools used for generic HRQOL and even disease specific measures may not capture the specific areas that affect HRQOL related to GC, such as self-esteem or mental health functions. We report significant variability of methods to document HRQOL. While the PedsQL-RM and PedsQL core-inventory were the most used, they often under-report areas related to self-esteem, and physical changes which impact patient satisfaction based on the ADR reports. Therefore, clinicians and future researchers need to consider
this in future design of studies looking at HRQOL impacts related to GCs. Moreover, given the broad spectrum of GC-related ADRs, single dimension HRQOL tools such as the QoML may not be as useful to identify the most significant areas of HRQOL impacts related to a systemic treatment such as GCs when compared to other tools utilizing multi-dimensional measures. To this end, multi-dimension HRQOL tools may be more appropriate in the future to evaluate the complexity of treatment related ADRs. Therefore, the prospective development of validated tools to measure and monitor these important parameters would be beneficial to study GC-related toxicity in childhood RD, work that is currently underway. Reducing the burden of disease and treatment-related damage is nevertheless important and would lead to improved patient outcomes.

GC-related ADRs are an important factor affecting HRQOL in children with RD, as these studies have shown that patients and families are concerned about the undesired complications of drug therapy. Only recently have clinicians developed methods to document GC-related ADRs. Of these, the pGTI provides the most specific definitions of GC-related ADRs. However, it has yet to be implemented as the standard way to document GC-related ADRs. Moreover, many of the seminal studies evaluated in this current review were published before pGTI was created. Therefore, due to a lack of standardized methods to document ADRs, it is likely that GC-ADRs in children with RD are significantly under-reported. This represents a significant limitation in describing the full-scale impact of GC-related ADRs on patient HRQOL.

Behavioral and emotional functioning ADRs are an important domain that may be difficult to capture unless clinicians ask about them specifically. Interestingly, there seems to be conflicting effects in terms of the impact of prednisone therapy on cognitive function: both worsening attention and improved executive function are reported, and it is unclear if this is due to the underlying disease process of lupus nephritis, or any neuropsychiatric symptoms, versus the actual effect of the GC-treatment. The ever-present tradeoff between increased functionality from GC immune modulation, the adverse side effects, and subsequent impact on HRQOL is apparent. Future studies need to be conducted to further delineate the impact of steroid treatment on long-term
cognitive outcomes while addressing underlying disease-related factors that may affect cognition.

In summary, the current evidence would suggest a moderate impact of GC-treatment on reported HRQOL in children and adolescents with RD. Impacts may be due to short-term and long-term side effects related to physical changes, emotional functioning, and cognition, but may also be due to long-term damage from both disease and prolonged GC-exposure. Ongoing efforts to include HRQOL measurements in studies that interrogate the burden of GC-treatment will allow clinicians to prioritize and integrate management for ADRs that may inform patient-centered treatment priorities for children with RD in the future.
Chapter 3

3  Body-mass-index associated with glucocorticoid-related weight gain in children with rheumatic disease on high-dose prednisone.

Prednisone is an important drug used as a first line therapy for moderate to severe presentations of childhood RDs. Prednisone is a pro-drug that is metabolized to prednisolone by the hepatic enzyme 11-B-HSD and is cleared from the body renally. Treatment with high-dose prednisone therapy in children is defined as 30 mg or standardized by ≥ 1 to 2 mg/kg/day, and moderate-dose prednisone is defined as 7.5 mg/day or greater. While some patients develop severe toxicity, others seem to be less susceptible to these events. Many children on long-term prednisone eventually experience GC-related ADRs. These include weight gain, high blood pressure, low bone-mineral density, as well as metabolic side effects, mood and sleep disturbances, and skin changes. Infections and increased mortality have also been associated to the number of days of exposure to GCs in children with ALL treated with standard chemotherapy protocols, regardless of dose and duration of GC treatment.

PK studies of prednisone in children have shown that standard weight-based doses result in large variations of drug concentrations in the blood. Clinical features such as serum albumin, renal function, obesity, age, and hepatic function, have been shown to affect the concentration levels and rate of clearance of medications in the blood. Pharmacokinetic modeling requires blood samples to be drawn at regular intervals and are often difficult to perform in large numbers of children due to the tolerability of procedures. Pain and anxiety related to procedures significantly impact pediatric HRQOL scores. Therefore, of the few studies of prednisolone pharmacokinetics, the small study sample sizes which makes it difficult to generalize to a population-based level.

We hypothesized that clinical variables that can affect pharmacokinetics of prednisolone, such as baseline body-mass-index (BMI), renal function (eGFR), transaminitis, and serum albumin levels, may be associated with risk for ADRs related to GC-toxicity. To evaluate which clinical variables may be associated with GC-related weight gain, a GC-
specific toxicity has been previously associated with PK parameters, we conducted a retrospective chart review to evaluate which clinical variables may be associated with more GC-related weight gain.

3.1 Methods:

We conducted a retrospective chart review for children \( \leq 17 \) years of age diagnosed with RDs at a single tertiary care academic pediatric rheumatology center. Patients seen between January 1, 2010 and December 31, 2020 were screened for exposure to moderate or high-dose prednisone therapy. Institutional research ethics board approval was obtained for this study (Appendix 2). Diagnoses included juvenile idiopathic arthritis (JIA), childhood systemic lupus erythematosus (cSLE), juvenile dermatomyositis (JDM), and chronic systemic vasculitis (SV) were included. Diagnoses were validated by a pediatric rheumatologist, and the maximum dose of prednisone was obtained based on paper documentation and electronic prescription. We included charts of patients who received moderate- to high-dose prednisone therapy for more than 90 days, with a minimum of four follow-up visits in a 12-month period. We used this definition for long-term GC treatment to capture the burden of long-term side effects that are seen with GC treatment.

Variables collected included age, gender, pubertal status, diagnosis, weight, height, blood pressure, and BMI with corresponding World Health Organization z-scores. Anthropomorphic data were collected at the time of GC initiation and at the time of maximum BMI z-score in the first 12 months of therapy. Baseline blood pressures (BP) with corresponding percentiles were recorded. Laboratory parameters collected at the time of initiation of GC treatment included urea, creatinine, urinary protein, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma glutamyl-transferase (GGT), and albumin. Estimated glomerular filtration rate (eGFR) was calculated using the pediatric Bedside Schwartz Equation. Systemic GC exposure was captured by collecting the dose, duration, intravenous therapy converted to oral prednisone equivalent dosing. Intravenous pulse GC therapy defined as 20-30 mg/kg/day (to a maximum 1000 mg) of intravenous methylprednisolone per dose was then converted to prednisone equivalents and included in the cumulative GC dosing in 12 months.
A standardized Glucocorticoid-Toxicity-Index (GTI) to capture the burden related to GC treatment was used, with adaptations for definitions for GC-related weight gain. We defined GC-related weight gain greater or equal to 20% of baseline weight. We fitted splines along a child’s growth curve, and subtracted the amount of weight gain that would be due to projected growth as per baseline z-score from the maximum amount of weight gained over a 12-month period. GC-induced hypertension was defined as new onset blood pressure readings greater or equal to 95th percentile on 3 separate visits, after the initiation of prednisone therapy.

ADRs were recorded over a 12-month period from the time GC therapy is started. Demographic data were summarized using means (standard deviations) and frequencies (percentages). Patient variables that affect pharmacokinetic profiles were chosen a priori to be evaluated as prognostic factors for GC-toxicity: age, eGFR, albumin, hepatitis, and baseline BMI-z-score were evaluated as predictors in separate logistic regressions for the development of ADRs including severe GC-toxicity, hypertension, infections, and fractures using. We conducted a complete case analysis; analyses were performed using SPSS v.26 (IBM Corp., Armonk, NY, USA), and p-values <0.05 were considered statistically significant.

3.2 Results:

The flow chart of chart selection is presented in Figure 3.1. Of the sixty-two patients included, most patients were female (55, 78.6%) and included 22 (29.3%) patients with cSLE, 22 (29.3%) with JIA (for which 18 patients were diagnosed with systemic JIA), 8 (10.7%) JDM, and 10 (13.3%) patients were diagnosed with systemic vasculitis. Mean (SD) age was 11.3 (4.4) years, with 38 (45.2%) patients in the early stages of puberty (Tanner 1 and 2). Mean (SD) WHO z-scores at baseline were 0.29 (1.47) for BMI, 0.32 (1.27) for weight and 0.01 (1.19) for height. Twenty-seven (39.1%) children received pulse methylprednisolone therapy as part of their treatment course.
Figure 3-1: Inclusion and Exclusion Criteria for Chart Review

103 charts reviewed

Prednisone > 3 months
n=85

No steroid or prednisone < 3 months
n=13

IV methylprednisolone only
n=5

Other diagnoses (IBD, HSP)

Rheumatic disease only
n=79

Inadequate data (incomplete chart data, follow up data, medication data)

n=17

Total charts included for analysis
n=62
Table 3-1: Baseline Characteristics of Pediatric Rheumatic Disease Cohort

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total rheumatic disease cohort (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis (no, %)</strong></td>
<td></td>
</tr>
<tr>
<td>cSLE: 22 (35.4)</td>
<td>JIA: 22 (35.4)</td>
</tr>
<tr>
<td>JIA: 22 (35.4)</td>
<td>sJIA: 18 (29.0%)</td>
</tr>
<tr>
<td>JDM: 8 (12.9)</td>
<td>Other: 10 (16.1)</td>
</tr>
<tr>
<td><strong>Age (mean years, SD)</strong></td>
<td>11.3 (4.37)</td>
</tr>
<tr>
<td><strong>Pre-pubertal (no, %)</strong></td>
<td>34 (54.8)</td>
</tr>
<tr>
<td><strong>Female (no, %)</strong></td>
<td>50 (66.7)</td>
</tr>
<tr>
<td><strong>Weight z-score (mean, SD)</strong></td>
<td>0.32 (1.37)</td>
</tr>
<tr>
<td><strong>Height z-score (mean, SD)</strong></td>
<td>0.01 (1.19)</td>
</tr>
<tr>
<td><strong>BMI z-score (mean, SD)</strong></td>
<td>0.29 (1.47)</td>
</tr>
<tr>
<td><strong>Serum albumin (mean, SD)</strong></td>
<td>36.3 (6.8)</td>
</tr>
<tr>
<td><strong>eGFR (ml/min/1.73m²)</strong></td>
<td>132 (60.3)</td>
</tr>
<tr>
<td><strong>Proteinuria (no, %)</strong></td>
<td>20 (26.7)</td>
</tr>
<tr>
<td><strong>Hepatitis (no, %)</strong></td>
<td>18 (26.1)</td>
</tr>
<tr>
<td><strong>MAS (no,%)</strong></td>
<td>8 (12.9)</td>
</tr>
</tbody>
</table>

**Prednisone Dosing Regimen**

| Maximum prednisone dose/kg (mg) (mean, SD) | 1.10 (0.46) |
| Cumulative prednisone dose *(mg/kg)        | 187.76 (120.37) |
| Average mg/kg/day *(mg/kg)                 | 0.57 (0.36) |
| Duration (days)* (mean, SD)                | 302 (95.24) |
| Other medications                         | Pulse methylprednisolone 26 (41.9) |
|                                          | Anti-epileptic 2 (3.2) |
|                                          | Vitamin D 29 (46.8) |
|                                          | Calcium 33 (53.2) |

SLE: systemic lupus erythematosus, sJIA: systemic juvenile idiopathic arthritis, JIA: other ILAR-JIA subtypes, JDM: juvenile dermatomyositis, Other: Blau, systemic vasculitis. MAS: macrophage activation syndrome, SD: Standard Deviation, eGFR: estimated glomerular filtration rate (Bedside Schwartz pediatric equation). Early puberty = Tanner Stage 1 or 2.

*over 12-month period

ADRs were common in this cohort of patients. Of 62 patients, 35 (56.5%) experienced more than 10% weight gain above projected growth, 11 (17.7%) developed new-onset obesity, and 15 (24.2%) met criteria for hypertension. The mean (SD) maximum percent weight gain was 21.1% (15.8), although the range reflects a wide variability (median 13.5%, IQR (8.1, 22.9). ADRs are summarized in Table 3-2. Vertebral fractures were included in the total number of fractures.
Table 3-2: Frequency of Adverse Effects in Children with Rheumatic Disease on Moderate to High-dose Glucocorticoid Treatment

<table>
<thead>
<tr>
<th></th>
<th>SLE</th>
<th>JIA</th>
<th>JDM</th>
<th>Other</th>
<th>All patients</th>
<th>Chi-squared p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain – 10% or greater (no, %)</td>
<td>14 (22.5)</td>
<td>10 (16.1)</td>
<td>5 (8.1)</td>
<td>6 (9.7)</td>
<td>35 (56.5)</td>
<td>0.634</td>
</tr>
<tr>
<td>Weight gain – 20% or greater (no, %)</td>
<td>9 (14.5)</td>
<td>8 (12.9)</td>
<td>4 (6.4)</td>
<td>2 (3.2)</td>
<td>23 (37.1)</td>
<td>0.580</td>
</tr>
<tr>
<td>Glucocorticoid-obesity (no, %)</td>
<td>5 (8.1)</td>
<td>4 (6.4)</td>
<td>2 (3.2)</td>
<td>0 (0)</td>
<td>11 (17.7)</td>
<td>0.420</td>
</tr>
<tr>
<td>Hypertension (no, %)</td>
<td>7 (11.2)</td>
<td>4 (6.4)</td>
<td>4 (6.4)</td>
<td>0 (0)</td>
<td>15 (24.1)</td>
<td>0.065</td>
</tr>
<tr>
<td>Infections (no, %)</td>
<td>10 (16.1)</td>
<td>7 (11.2)</td>
<td>3 (4.8)</td>
<td>4 (6.4)</td>
<td>24 (38.7)</td>
<td>0.832</td>
</tr>
<tr>
<td>Fractures (no, %)</td>
<td>2 (3.2)</td>
<td>2 (3.2)</td>
<td>2 (3.2)</td>
<td>1 (1.6)</td>
<td>7 (11.3)</td>
<td>0.630</td>
</tr>
<tr>
<td>Vertebral fractures (no, %)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
<td>3 (4.8)</td>
<td>0.437</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>28</td>
<td>8</td>
<td>10</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>

Baseline BMI z-scores were positively associated with the development of glucocorticoid-related weight gain greater than 20% (OR=2.346, 95% CI=1.389 - 3.961, p=0.001). There was no association with severe GC-toxicity and serum albumin, eGFR, hepatitis and maximum dose/kg with severe GC-toxicity. Exploratory analysis of the possible association between clinical variables and other ADRs (hypertension, infections) was not significant (p>0.05).

### 3.3 Discussion

Based on our study, children with higher baseline BMI are more likely to develop GC-related weight gain within 12 months of treatment with prednisone. Previous studies in adults have demonstrated that prednisone PK are altered in patients with increased BMI but this relationship had not yet been established in children with RD. Increased BMI may be associated with a higher percentage of body fat, which may affect the volume of distribution of GCs in the body. Using a purely weight-based dosing approach may not
account for differences in dosing between lean body mass and total body mass. Furthermore, the variation in serum concentrations of prednisolone in the blood varies between patients despite standardized weight-based dosing which may also indicate variability in PK parameters (e.g., volume of distribution) that may be related to differences in body mass composition.

Our study reports a higher frequency of ADRs compared to the current literature. For instance, previous studies have reported that the frequency of GC-related weight gain was reported as around 20% for all doses of long-term GC treatment, while almost half our cohort had GC-related weight gain. The patient population is likely at higher risk of ADRs due to higher doses and longer duration of GC treatment indicated for the treatment of childhood ED. The use of BMI itself has limitations, as it may not reflect the changes in body mass composition. Prolonged treatment with GCs in children with JDM is associated with increase in percent total body fat despite minimal changes in BMI. Future studies studying GC-related weight changes should account for changes in body-mass composition, as this may ultimately affect the burden of GC-related ADRs in these patient populations.

More recently, the pGTI defined GC-related weight ADRs using raw cut-offs for BMI units to describe toxicity. We chose a different approach than the pGTI to define our GC-related weight gain in the context of the patient’s individual growth trajectory by fitting splines on their growth curve and estimating the eventual growth of each individual patient. We felt this accounted for weight changes due to growth, which change over time during a child’s development, rather than a raw cut-off. Our methods should be more sensitive to detecting children who may gain a significant amount of weight, but who may not meet criteria for obesity.

Our study was limited by the small sample size and the retrospective nature of the data collection. We were unable to fully capture the burden of ADRs such as infections, hypertension, and metabolic derangements, which would also be important for clinicians who treat these disorders. Standardized disease activity measures were not collected routinely as part of these visits, which is another limitation of the study as disease activity
may affect organs involved in drug metabolism such as the liver and kidneys. Due to the significant proportion of females in this study, we were unable to examine the role biological sex-based as a risk factor for the development of GC-related toxicities.

This initial study has provided interesting clues to children who may be at greatest risk of GC-related weight gain. Higher BMI may reflect higher proportions of body fat, which may ultimately affect pharmacokinetics for these patients. Whether patients with higher BMI may benefit from lean-body mass dosing remains to be seen. Further studies are needed to establish optimal dosing strategies, possibly using lean-body mass dosing strategies, to mitigate this risk. The burden of GC-related weight gain justifies strategies to minimize prolonged exposure to GC in patients, and to determine the optimal counseling and behavioral interventions that may mitigate this risk.
Chapter 4

4 Pharmacokinetic monitoring of prednisolone in children with rheumatic diseases: a feasibility study

In Canada, the prevalence of childhood chronic RD is estimated to be between 8.0-11.7 per 10,000 individuals over a 10-year period, with 10-15% of these children requiring long-term treatment with prednisone.\(^1\,^2\) Prednisone is an oral GC medication that is metabolized to the biologically active molecule, prednisolone, by the 11β-HSD1 enzyme in the liver. Prednisolone initiates transcriptional events related to down-regulating inflammation but also cellular processes that are associated with ADRs.\(^10\,^11\) Children with RD such as cSLE, JDM and SV often require oral prednisone at high dose defined as \(\geq\) 30 mg per day, or 1-2 milligram per kilogram per day for moderate to severe disease presentations, with a significant proportion remaining on therapy for several months.\(^74\)

While patients and caregivers are tolerant to some ADRs to gain disease control,\(^32\) long-term prednisone therapy has been associated with additionally burdensome ADR including excessive weight gain, cataracts, growth suppression, osteoporotic insufficiency fractures, neuropsychiatric effects on mood and sleep, reduced satisfaction with treatment, and reduced HRQOL.\(^44\,^81\) Although initial studies of prednisone in healthy children have revealed significant variability in systemic exposures and PK parameters especially at higher doses,\(^82\) no studies have examined the relationship between circulating drug concentrations in children with RD and dose-response, patient-reported ADRs, and toxicity. In addition, the ideal timing of sampling for plasma prednisolone concentrations for incorporation into routine clinical practice has not been established. Therefore, dose-response and toxicity-thresholds must be determined before therapeutic drug monitoring (TDM) is possible.

PK monitoring measures the medication levels in the blood of patients and describes the changes of these concentrations over time as a function of the absorption, bioavailability, distribution, and elimination by the body.\(^13\) Previous PK studies of prednisolone in SLE demonstrated a possible relationship between drug concentrations in the blood (higher area-under-the curve (AUC)) and lower disease activity.\(^23\) Plasma concentrations for total and unbound prednisolone are surrogate measures of target tissue exposure, since the
circulating drug is delivered to target tissues for therapeutic effect.\textsuperscript{14} To date, there has yet to be a study that evaluates the relationship between plasma concentrations of prednisolone and the frequency of ADRs such as GC-related ADR, such as weight gain in children with RD. The absence of widely available and feasible PK standard operating procedures for children has precluded the development and implementation of TDM for prednisolone in the pediatric population.

Given the wide range of ADRs associated with GC-toxicity, it is unknown which ADRs have a dose-dependent response that can be captured by monitoring plasma drug levels. Data from pharmacokinetic sampling in adults suggest that patients with higher blood concentrations may be at greater risk of developing a Cushingoid appearance in renal transplant patients,\textsuperscript{18} GC-related physical changes is one of the most bothersome ADRs to patients and inter-patient variability in the frequency of development of these ADRs is considerable despite weight-based dosing, furthering the understanding of PK parameters associated with prednisolone toxicity will be valuable.

To develop strategies to explore these we undertook a study to define the feasibility of PK studies of glucocorticoids in children. Accordingly, we developed a study protocol to prospectively evaluate the association of PK serum concentrations with the development of GC-induced toxicity, notably targeting the feasibility and reliability of a sparse PK sampling strategy in a cohort of pediatric patients diagnosed with chronic RD that require moderate to high-dose prednisone for at least 6 months. Given our findings from the retrospective cohort study (Chapter 3), we hypothesized that children with greater concentrations of prednisolone in their blood at specified time-points would be at increased risk of developing GC-related weight gain. Herein, we report the feasibility parameters of our protocol, as well as the initial findings of our pilot study.

4.1 Methods

We conducted a prospective pilot study at a single academic pediatric rheumatology center. We recruited patients ages 5 to 17 diagnosed with RDs such as JIA as per International League of Against Rheumatism (ILAR) classification,\textsuperscript{83} SLE as per ACR classification criteria,\textsuperscript{84} JDM as per Peter and Bohan’s criteria,\textsuperscript{85} and systemic vasculitis
per Chapel Hill criteria. Eligible patients were starting treatment with high-dose prednisone treatment (30 mg or ≥ 1 mg/kg/day). Institutional ethics board approval was obtained (Appendix 3). Patients were excluded if they were not able to provide voluntary informed consent.

Clinical variables collected at time of diagnosis included age, biological sex, diagnosis, albumin, presence of nephritis, and disease activity scores by physician global assessment (PGA) at the time of diagnosis. Weight, height, and BMI measures were obtained at the time of starting prednisone treatment, and 3 and 6 months after prednisone treatment. Weekly medication data was verified at 0 to 6 months to obtain cumulative prednisone dose as per documentation electronic medical record prescriptions. ADR profiles were collected by a standardized questionnaire administered at 1 month after starting prednisone treatment and at 6 months (Appendix 4). Patients were contacted by e-mail 1 week before the 6-month mark with questionnaires and ADRs. ADRs were administered at a clinic visit a week later or by phone or email as per participant preference. We recorded the following ADRs: weight gain, vomiting, nausea, diarrhea, constipation, mood changes, behavior changes, skin changes, sleep disturbance, infections, headache, and glaucoma.

PK sampling for trough (prior to dose) and peak (2-hour post-dose) prednisolone concentrations at steady-state were obtained after patients were taking the same dose of prednisone for at least 7 days. Time for peak level sampling was determined based on previously reported PK profiles in cSLE patients. Blood samples were stored at 4°C prior to centrifugation at 2000 g for 10 minutes at 4°C and centrifuged within 6 hours of collection. Separated plasma was aliquoted into 150 µL samples and stored in plastic cryotube using a new, clean pipette for every sample. All samples were stored at -80 °C until analysis. Each sample was labelled for the study ID number, aliquot number, and time of sampling, and analyte to be assayed. Specimen logs were completed for all samples. Samples were analyzed at the University of Western Ontario, London, Ontario, Canada.
Quantitation of Prednisolone in Plasma

Serum concentrations of prednisolone were determined using high-pressure liquid chromatography-mass spectrometry (HPLC-MS/MS). Plasma samples (25 µL) were spiked with 10 µL of dexamethasone (1 µg/mL in acetonitrile). After the addition of 75 µL of ice old acetonitrile and vortexing, the protein pellet was separated by centrifugation at 10,000 g at 21 °C for 10 minutes. The supernatant was dried prior to reconstituting with 50 µL of methanol. 40 µL of this solution was mixed with 160 µL of Mobile Phase A (5 mM ammonium acetate in water, pH 4 with acetic acid, and 50 µL of this mixture was injected into Agilent 1100 liquid chromatograph (Thermo Scientific, San Jose, California). Standard curve samples were prepared from control plasma (25 µL) spiked with prednisolone (0 to 2000 ng/mL final concentration) and dexamethasone as previously described. Prednisolone and dexamethasone were sourced from Sigma (St. Louis, Missouri).

Analytes were separated using reverse-phase chromatography using a Thermo Hypersil Gold C18 column (50 x 5 mm, 5 µm, Thermo Scientific). Mobile phase was delivered at a flow rate of 0.5 mL/min with gradient flow with Mobile phase A and acetonitrile. For the first 30 seconds, the mobile phase consisted of 20% acetonitrile, and then increased linearly over 4 minutes. After 1 minute at 90% acetonitrile, there was a linear decrease to 20% acetonitrile which was held for an additional 30 seconds. The retention times for prednisolone and dexamethasone were 2.6 and 3.6 minutes, respectively.

Analytes were detected by MS/MS on a Thermo TSQ Vantage triple quadrupole instrument (Thermo Scientific) equipped with heated electrospray ionization probe (HESI-III) set with probe voltage (3000 V), vaporizer temperature (350 °C), sheath gas (8 arbitrary units) and auxiliary gas (4 arbitrary units). The following multiple reaction monitoring transitions were used with detection in negative mode and collision gas (1.5 mTorr): prednisolone (419.0 → 329.1 m/z), dexamethasone (451.0 → 361.3 m/z) with collision energy at 20 V and 19 V respectively. Standard curves were linear (R² > 0.97).

Statistical analysis:
Descriptive analysis was performed for age, sex, diagnoses, and prednisone dose at enrollment, as well as laboratory parameters collected every 3 months including: albumin level, and presence of proteinuria (urine dipstick > 1+ protein). Continuous variables were summarized using means and standard deviations (or medians and interquartile ranges for non-normal distributions), and categorical variables summarized using frequencies and percentages.

Due to the small sample size of the pilot group, an exploratory analysis to examine the relationship between PK parameters and prednisolone related weight-gain (percent BMI change above baseline BMI) was performed using linear regression analysis and Student’s t-test respectively. Analyses were performed using SPSS v.27 (IBM Corp., Armonk, NY, USA), and p-values <0.05 was considered statistically significant.

### 4.2 Results

Study flow is summarized in Figure 4-1. Patients were approached during clinic visits within 2 months of diagnosis and starting prednisone treatment. Seven of nine patients were successfully consented for the study. Reasons for declining included fear of additional phlebotomy (n = 2), and additional time required for PK sampling (n =1). PK sampling was performed within 14 days of consistent once daily dosing of 1 mg/kg/day of prednisone. One patient was excluded from analysis as they had taken their dose of prednisone prior to PK sampling, and there was no additional opportunity to sample while on the eligible dosing. All blood samples were successfully obtained for the 6 patients who had consented who were eligible for the sampling.

Patients were contacted at 6 months by electronic mail or telephone depending on indicated preference, and followed by an in-person clinic visit to ensure the responses were obtained. Side effect and HRQOL questionnaires were sent via e-mail a week before. Of the remaining 6 patients (66.7%) all HRQOL questionnaires were completed at 6 months. No participants were lost to follow up. Only one patient had discontinued GC treatment by 6 months.
Figure 4-1: Pharmacokinetic study for children with rheumatic disease on high-dose glucocorticoid therapy

Patients presented in moderate to severe activity (PGA scores > 4/10), and baseline characteristics are summarized in Table 4-1. Patients were diagnosed cSLE, JDM, sJIA and systemic vasculitis. The mean dose range meeting criteria for high-dose GC treatment was 49.7 mg (range 25 mg to 50 mg per day), or 0.92 mg/kg/day (0.55 mg/kg to 1.12 mg/kg per day). The mean peak concentration was 1255.9 ng/mL (SD 520.2 ng/mL) and trough 17.7 ng/mL (13.8 ng/mL). Prednisone dosing is summarized in Table 4-2, and concurrent medications in Table 4-3. Significant variability was still reported after normalizing for weight-based dose with the mean peak prednisolone concentration 1342.7 ng*kg/mL*mg (SD 386.8 ng*kg/mL*mg) and trough concentration 22.3 ng*kg/mL*mg (SD 20.5 ng*kg/mL*mg). Concentrations are reported in Table 4-4. 53

Table 4-1: PK Study Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Diagnosis</th>
<th>PGA score</th>
<th>Sex</th>
<th>Proteinuria &gt; 1.0 g/mL</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td>13</td>
<td>cSLE</td>
<td>10</td>
<td>F</td>
<td>Y</td>
<td>74</td>
<td>170</td>
<td>25.6</td>
</tr>
<tr>
<td>115</td>
<td>12</td>
<td>sJIA</td>
<td>6</td>
<td>F</td>
<td>N</td>
<td>48.9</td>
<td>162</td>
<td>18.59</td>
</tr>
<tr>
<td>117</td>
<td>11</td>
<td>c-ANCA vasculitis</td>
<td>6</td>
<td>F</td>
<td>Y</td>
<td>41.2</td>
<td>152</td>
<td>17.83</td>
</tr>
<tr>
<td>119</td>
<td>12</td>
<td>TB-arteritis</td>
<td>7</td>
<td>F</td>
<td>N</td>
<td>36.7</td>
<td>160</td>
<td>15.47</td>
</tr>
<tr>
<td>121</td>
<td>5</td>
<td>JDM</td>
<td>8</td>
<td>F</td>
<td>N</td>
<td>20.2</td>
<td>114</td>
<td>16.54</td>
</tr>
<tr>
<td>123</td>
<td>16</td>
<td>cSLE</td>
<td>4</td>
<td>M</td>
<td>Y</td>
<td>52.1</td>
<td>168</td>
<td>18.46</td>
</tr>
</tbody>
</table>
Table 4-2: Prednisone Dosing Data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prednisone at time of PK (mg)</th>
<th>Maximum Prednisone dose (mg)</th>
<th>Cumulative dose 6 months (mg)</th>
<th>Average daily dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>60</td>
<td>16760</td>
<td>226.5</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>60</td>
<td>68790</td>
<td>1427.2</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>60</td>
<td>6821</td>
<td>165.6</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>60</td>
<td>14560</td>
<td>396.7</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>40</td>
<td>20980</td>
<td>1038.6</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>60</td>
<td>7820</td>
<td>150.1</td>
</tr>
</tbody>
</table>

*Doses at time of PK sampling. Cumulative doses calculated based on chart review, and average daily dose normalized to baseline weight at time of starting high-dose prednisone treatment.

Table 4-3: Concurrent medications a time of PK sampling.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of patients (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIG</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td><strong>Biologics:</strong></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td><strong>Immunosuppressants</strong></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>Plaquenil</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim Sulfamethoxazole</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>1 (16.7%)</td>
</tr>
</tbody>
</table>

All patients were taking additional medications at time of PK sampling.

Table 4-4: Plasma and peak concentrations of prednisolone

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg)</th>
<th>Weight (kg)</th>
<th>Weight based dose (mg/kg)</th>
<th>Peak (ng/mL)</th>
<th>Trough (ng/mL)</th>
<th>Weight normalized Peak (ng<em>kg/mL</em>mg)</th>
<th>Weight normalized Trough (ng<em>kg/mL</em>mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>73</td>
<td>0.55</td>
<td>616.7</td>
<td>30.1</td>
<td>1125.5</td>
<td>54.9</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>54</td>
<td>0.83</td>
<td>1034.9</td>
<td>7.5</td>
<td>1241.9</td>
<td>9.0</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>51.9</td>
<td>0.96</td>
<td>1854.7</td>
<td>34.4</td>
<td>1925.2</td>
<td>35.8</td>
</tr>
</tbody>
</table>
The mean dose range meeting criteria for high-dose GC treatment was 49.7 mg (range 25 mg to 50 mg per day), or 0.92 mg/kg/day (0.55 mg/kg to 1.12 mg/kg per day). The mean peak concentration was 1255.9 ng/mL (SD 520.2 ng/mL) and trough 17.7 ng/mL (13.8 ng/mL). Significant variability was still reported after normalizing for weight-based dose with the mean peak prednisolone concentration 1342.7 ng*kg/mL*mg (SD 386.8 ng*kg/mL*mg) and trough concentration 22.3 ng*kg/mL*mg (SD 20.5 ng*kg/mL*mg).

ADRs were common. All patients experienced increased appetite, and few had gastrointestinal symptoms such as nausea or vomiting. The most frequent ADR was weight gain, affecting 5 of 6 patients. Two patients experienced skin changes such as striae and acne, and one experienced hirsutism during high-dose periods. Four of six patients reported mood swings, and half had behavioural changes that they reported. Half of the patients also experienced headaches. In terms of other important side effects, one patient experienced two severe infections during her initial treatment phase: cytomegalovirus infection that required hospitalization for supportive care and a urinary tract infection that was treated with antibiotics. ADRs are summarized in Table 4-5.

<table>
<thead>
<tr>
<th>ADR</th>
<th>Number of patients (n= 6)</th>
<th>% total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased appetite</td>
<td>6</td>
<td>100 %</td>
</tr>
<tr>
<td>Weight gain</td>
<td>5</td>
<td>83.3 %</td>
</tr>
<tr>
<td>Mood swings</td>
<td>4</td>
<td>66.7%</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>50%</td>
</tr>
<tr>
<td>Behaviour change</td>
<td>3</td>
<td>50%</td>
</tr>
<tr>
<td>Acne</td>
<td>2</td>
<td>33.3%</td>
</tr>
<tr>
<td>Striae</td>
<td>2</td>
<td>33.3%</td>
</tr>
<tr>
<td>Abdominal discomfort/Nausea</td>
<td>1</td>
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</tr>
<tr>
<td>Hirsutism</td>
<td>1</td>
<td>16.7%</td>
</tr>
<tr>
<td>Sleep disturbance</td>
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<td>16.7%</td>
</tr>
<tr>
<td>Cognitive impairment</td>
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<td>16.7%</td>
</tr>
<tr>
<td>----------------------</td>
<td>---</td>
<td>-------</td>
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<tr>
<td>Infections (self-reported)</td>
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**Number Adverse Effects Reported**

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<th>Percentage</th>
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</tr>
<tr>
<td>5</td>
<td>3</td>
<td>50%</td>
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</table>

ADR- adverse drug reaction

We summarize the changes in BMI in Table 4-7. Mean weight gain is 10 kg from baseline, or 22.7% while on high-dose prednisone treatment. Most patients on high-dose steroid experienced significant decreases in disease activity, with a mean decrease of 3.9 PGA units at 6 months.

Figure 4.2 summarizes the exploratory analysis which demonstrates a moderate linear relationship between weight-based dosing and peak prednisolone concentration ($R^2=0.6154$) (4.2A) and lack of linear relationship to body-surface-area based dosing ($R^2=0.035$) (data not shown). In terms of the relationship between peak concentrations and BMI curves, interestingly, patients with lower peak concentrations may still be at risk of developing significant BMI change (Figure 4.2B - this would suggest that peak plasma concentrations alone may not be sufficient to describe the overall exposure to the GCs and subsequent risk for GC-toxicity. Dual X-ray Absorptiometry (DEXA) scans and therefore we were unable to obtain the percentage of body fat to calculate lean body mass. Student’s unpaired t-test performed between 3 patients with the greatest increase in BMI and those with the 3 lowest changes in BMI did not show statistically significant differences between peak plasma concentrations ($p>0.05$) (Figure 4.2C). This may be in part explained by the variability due to differences in the actual cumulative doses between patients, as some patients were initially on higher doses than 1 mg per kg to start, and PK testing was not necessarily taken at the highest GC dose taken by patients. Interestingly, our data would suggest an inverse relationship between peak concentration of prednisolone and change in disease activity over 6 months (Figure 4.2D). Once again, the timing of the PK sampling, which may have not been taken during the highest dose
taken by the patient, may under-estimate the actual cumulative exposure to prednisone than captured by the PK data.

Table 4-6: BMI, weight and disease activity changes at baseline and at 6 months

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<th>Weight 6 mo</th>
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<th>Δ Weight (kg)</th>
<th>Δ BMI kg/m²</th>
<th>% Wt</th>
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<td>19.57</td>
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<td>4.1</td>
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<tr>
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<td>2.0</td>
<td>1.1</td>
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</table>

BMI - body-mass-index.  
PGA - Physician Global Assessment (Disease Activity Scores)

Figure 4-2: Relationships between peak prednisolone concentrations as a function of mg/kg body weight, and BMI changes, and disease activity
A. We summarize the exploratory analysis demonstrates a moderately linear relationship between weight-based dosing mg/kg and peak prednisolone concentration ($R^2=0.6154$). B. Relationship between peak concentration (normalized to weight-based dose) and change in BMI ($R^2=0.2995$). C. We compared the three patients with the most weight gain (blue box) with the three who experienced less weight gain (gray box), and mean concentration was greater in the group with the higher BMI, although it did not meet statistical significance ($p>0.05$). X denotes the mean peak prednisolone concentration and the box – the range of concentrations observed. D. Disease activity scores as expressed by physician global assessment scores (PGA), with a maximum score of 10, in comparison to peak concentrations of prednisolone are shown with moderate inverse linear relationship demonstrated.

### 4.3 Discussion

High-dose prednisone therapy is associated with significant morbidity in children with RD. We describe a pilot study of 6 children, the majority of whom developed side effects from treatment with 83% meeting criteria for GC-related weight gain based on the most-recent pGTI.\textsuperscript{28} To our knowledge, no previous study has been performed to explore the feasibility of studying the relationship between prednisolone pharmacokinetics and ADRs such as GC-related weight gain in this population.

We demonstrated the feasibility of this approach to study these questions in children, with successful enrolment of 77% of patients approached (limited sample size). We were able to make several key observations. We showed that despite weight-based dosing, significant variability in serum prednisolone concentrations is demonstrated between patients taking high-dose prednisone, which may be due to differences in volume of distribution related to relative adiposity. While traditionally allometric scaling of
prednisone dosing is based on weight, at higher doses, our data suggest that weight-based dosing demonstrates a more linear relationship with the peak concentration achieved than body surface area-based dosing. There is some evidence that body-surface area dosing leads to greater cumulative doses of prednisone, and that weight-based dosing is equally effective, for other pediatric chronic disease populations such as nephrotic syndrome.87 As prednisolone is highly lipophilic, other dosing approaches such as lean-body weight dosing should also studied in the future to improve the precision of peak concentrations achieved in the blood, especially in patients who are obese.88 The effects of the underlying disease may also contribute to differences observed in PK parameters on high-dose regimens. The patient with the lowest peak observed is diagnosed with JDM, which has been previously described to have effects on delayed intestinal absorption that may affect bioavailability despite being on the same weight-based dosing.46 This patient also had the lowest amount of weight gain over a 6-month period.

Pharmacokinetic monitoring in children for prednisolone has been challenging due to multiple blood samples and additional time required for sampling to be done on an outpatient basis. With a peak-trough sampling strategy, we were unable to reliably calculate additional pharmacokinetic parameters that describe the amount of prednisolone in the blood over time using preferred parameters such as the area under the curve (AUC), clearance, and elimination half-life. While our study protocol allowed for successful enrolment and sampling, the limited sample approach will not be adequate for future studies. Full characterization including AUC will be necessary to define the relationship between prednisolone concentrations in the blood and the risk for GC-based weight gain, as we suspect that ADRs require prolonged exposure to tissues to induce transcriptional changes that lead to the effects observed over the medium and long-term.

Although a small number of patients have been studies, we did observe that frequent blood sampling may not be acceptable to a pediatric study population. Two of nine patients declined sampling due to need for additional phlebotomy. This pilot study has informed future work to establishing the validity of non-invasive PK monitoring, such as the use of salivary sampling to measure prednisolone in the pediatric RD population.89
Nevertheless, this protocol demonstrates that collection of peak- and trough-levels are feasible in this patient cohort, and that they correlate reasonably with body-surface area and weight-based dosing. Further work is needed to understand the factors that lead to the variability, and whether patients who demonstrate higher concentrations of prednisolone in the blood are at risk for more severe ADRs.

Polypharmacy in children with RD presents an important challenge to PK studies. Patients and families often find it difficult to determine if ADRs are due to prednisone instead of the other medications that are prescribed. There are currently several tools such as toxicity indexes specific to GCs, such as the pGTI and QUEST tools,\textsuperscript{33,42} and patient reported outcome measures to this effect as well.\textsuperscript{45} However, they have yet to be validated and implemented in the clinical setting. Tools such as these are increasingly important to evaluate a growing area of literature that GC-toxicity plays a major impact on quality-of-life measures for pediatric patients with chronic RD.

While rare, childhood RD that requires treatment with prednisone is associated with significant short- and long-term morbidity. Understanding biomarkers and developing methods to improve the safety profile of GCs is of utmost importance to further improve the safety profile of GC medications such as prednisone.
Chapter 5

5 Conclusion

GC therapy remains a mainstay in the treatment of moderate-severe presentations of RDs in children. While efficient, clinicians and patients are wary of the potential for common and bothersome ADRs. The combination of therapeutic efficacy, cost, and availability, without alternatives for treatment for some RDs, means clinicians will continue to use GCs in the treatment of RDs for years. Clinicians and researchers are trying to decrease the burden of GC therapy by exploring different weaning protocols as well to decrease the cumulative dose of GC therapy. There is no consensus of how clinicians should wean, or tailor dosing, and there is little information to guide clinicians to this effect.

In the first part of the thesis, we looked at the concept of HRQOL and how GC-treatment affects HRQOL in children with RD. The neuro-psychiatric side effect profile of GCs may contribute to psychiatric symptoms which may subsequently have negative impact on patient HRQOL in domains related to mood and sleep. The neurodevelopmental changes during childhood may contribute to the risk of neuropsychiatric ADRs related to GC-treatment. Adolescents prescribed bed GC-treatment for instance reported lower HRQOL than adults with cSLE in the same study, which correlated with the GC-dose. Therefore, it is likely that GC-related ADRs have a negative impact HRQOL in children and adolescents with RD. While some clinicians feel that GC ADRs are unavoidable, others are starting to incorporate GC-related patient reported outcomes as primary outcome measures. This approach ensures that these study protocols can evaluate and decrease the burden related to GC-treatment. The development of GC-specific outcome measures, including HRQOL and ADR measurement tools specifically adapted to GCs represent an important advance in standardizing the nomenclature for toxicity. Ideally, HRQOL tools to evaluate GC related ADR should describe multiple domains to enrich our understanding of which domains may impact patient defined priorities.

Clinicians have observed that children who require high-dose GC treatment are at higher risk for ADRs compared to adults. From the perspective of obesity, our study suggests that the baseline BMI of children affects the risk of developing severe GC-induced
weight gain. All patients that had growth suppression were on high-dose therapy. This is important as it may suggest that tissues are differentially sensitive to the metabolic effects of supraphysiologic GCs.\textsuperscript{92,93} Further, in-vitro testing would be needed to confirm this and may suggest that alternative weight-based dosing strategies such as lean body weight dosing may be more appropriate in children with higher BMI.

We evaluated the risk for GC-toxicity by developing a protocol to study prednisolone PK in children with RD. What is known about PKs of prednisolone in children is that there is significant variability of prednisolone concentrations in the blood despite weight-based dosing. Age affects the metabolism of prednisolone, and younger children tend to metabolize the medication faster leading to an earlier peak and shorter half-life, especially in toddlers. Sex-differences in drug metabolism are suspected due to the presence of different sex steroids, but the reality is that much of the earlier PK work done in children consisted of small sample sizes did not account for sex.\textsuperscript{45,46,94} Lastly, disease states also affect the characteristics of pharmacokinetic parameters as we had discussed, with diseases such as JDM, where gastrointestinal dysfunction may lead to decreased motility, a later peak, but comparable half-life.\textsuperscript{46}

Our pilot study observations of PKs in children are interesting – those patients have high prednisolone concentrations in their bloods, tend to have greater degrees of GC-related weight gain. Since our sample size was small, the results did not reach statistical significance. However, we demonstrate that a PK study for children with RD can achieve adequate enrollment and acceptability, and that most patients will tolerate PK study procedures. While we do not currently have enough data for a personalized medicine approach in children with RD on high-dose GC therapy yet, our data demonstrates variability that is observed despite weight-based dosing. This may suggest that PK monitoring may be a viable option to identify patients at high risk for GC-related ADR. Further studies examining the clinical implications of this variation are needed.

The study of GC-toxicity is gaining momentum as a significant research priority in RDs, and children are well-positioned to benefit from this work as they have a higher risk of developing ADRs and often have high cumulative exposure than their adult counterparts.
Future directions for our study will include building on our pharmacokinetic modelling of prednisolone to include additional sampling. This would allow our team to establish PK parameters associated with systemic exposure, such as area-under-the-curves, plasma half-life, and clearance. Ideally, a limited sampling strategy will be used to obtain these parameters. Secondly, recognizing the difficulties in obtaining repeated phlebotomy, especially in sick and young children, non-invasive monitoring of prednisolone in other body fluids such as saliva or urine may also be feasible. There is some foundational work that has been established in nephrotic syndrome that would suggest an excellent correlation between saliva and plasma levels of prednisolone.89,95

GC stewardship is critical to ensure that patients with childhood RDs experience a lower burden of GC-toxicity over their lifetime. GCs remain affordable, accessible, and effective, and therefore, strategies to promote their safe dosing, especially in those who are at significant risk of experiencing ADRs will positively affect patient care outcomes in many resource contexts. Working towards dosing strategies that minimize side effect profiles will be the way of the future to support HRQOL for these children with lifelong RDs.
References


https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

doi:http://dx.doi.org/10.1038/nrrheum.2011.38

doi:10.1007/s11914-014-0228-x

doi:10.1093/jpepsy/jsj014


doi:https://dx.doi.org/10.1002/acr.24610


96. Demerath EW, Schubert CM, Maynard LM, et al. Do changes in body mass index percentile reflect changes in body composition in children? Data from the Fels...


Appendices

Appendix 1: Literature Search Strategy

LITERATURE SEARCH RESULTS

DATE: May 9, 2022
FOR: Dr. Renee Pang
FROM: Darren Hamilton (Ext. 75934)
SUBJECT: Steroid Search Strategy Focusing on Children with Rheumatic Disease
DATABASE USED: Ovid MEDLINE(R) ALL 1946 to May 06, 2022
PUBLICATION TYPES: All
LIMITS: None
RECORDS RETRIEVED: 652

Search Strategy and Results

Database: Ovid MEDLINE(R) ALL <1946 to May 06, 2022>
Search Strategy:

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2. Dermatomyositis/ (8663)
3. Arthritis, Juvenile/ (11236)
4. Rheumatic Diseases/ (24223)
5. Scleroderma, Systemic/ (21113)
6. Connective Tissue Diseases/ (7066)
7. Undifferentiated Connective Tissue Diseases/ (124)
8. Systemic Vasculitis/ (587)
9. Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/ (2466)
10. Arteritis/ (5204)
11. Takayasu Arteritis/ (4412)
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or/1-12 (179937)
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27 25 and 26 (52)
Appendix 2: Retrospective Chart Review Research Ethics

Dear Dr. Michael Redor,

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WIEM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

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No deviations from, or changes to, the protocol or WIEM application should be initiated without prior written approval of an appropriate amendment from Western HSREB, except when necessary to eliminate immediate hazards to study participants or when the change involves only administrative or logistical aspects of the trial.

All HSREB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is registered in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonization: Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 1 of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number REB 000000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Karen Copland, Ethics Officer on behalf of Dr. Philip Jones, HSREB Vice Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Appendix 3: Research Ethics Approval Pharmacokinetic Study

Dear Dr. Roberta Berard

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

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No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB, except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with and is constituted in accordance with, the requirements of the TriCouncil Policy Statement Ethical Conduct for Research Involving Humans (TCPS 2), the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH-GCP), Part C, Division 3 of the Food and Drug Regulations, Part 4 of the Natural Health Products Regulations; Part J of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 000000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Daniel Wyzynski, Research Ethics Coordinator, on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Appendix 4- Side Effect Questionnaire

**Study Name:** Characterizing Risk Factors for Adverse Effects in a Pediatric Cohort of Patients Requiring High-Dose Corticosteroid Treatment: A Pilot Study

**Study ID Number:** 111984

What medical conditions does your child have?
1. _____________________________________________
2. _____________________________________________
3. _____________________________________________
4. _____________________________________________

**Current medications:**
- ☐ Prednisone
- ☐ Naproxen
- ☐ Tylenol
- ☐ Inhaler
- ☐ Other __________________

**Current Dose Prednisone:** ___________________________________________________

Since your child’s last visit, have they experienced any of the following side effects?
- ☐ Weight gain
- ☐ Constipation
- ☐ Mood swings
- ☐ Vomiting
- ☐ Black or bloody stools
- ☐ Sleep disturbance
- ☐ Abdominal pain
- ☐ Skin changes
- ☐ Behaviour change
- ☐ Abdominal discomfort
- ☐ Eye pain
- ☐ Infection (describe):
- ☐ Nausea
- ☐ Headache
- ☐ Other (Please describe):

Has your child required any of the following in the last 2 weeks? (please check which apply)
- ☐ Hospital admission
- ☐ Emergency department visit
- ☐ Family Physician visit

*Thank you for choosing to participate in our study!*

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<th>Office Use Only:</th>
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Curriculum Vitae

Name: Renee Xin-Wei Pang

Post-secondary Education and Degrees:
University of Toronto
Toronto, Ontario, Canada
2003-2007 Bachelor of Arts (High Distinction)

University of Toronto
Toronto, Ontario, Canada
2007-2008 Master of Arts (French Literature)

Queen’s University
Kingston, Ontario, Canada
2009-2013 Doctor of Medicine

Western University
London, Ontario, Canada
2013-2018, Clinical Investigator Program

Honours and Awards:
Translational Research Grant (2019)
Department of Psychiatry Internal Seed Grant (2022) – Co-Principal Investigator

Related Work Experience
Paediatrician, London Health Sciences Centre
2018-present

Publications:


