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Learning the Hard Way: Clinical Trials in Juvenile Idiopathic Arthritis

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Learning the hard way: clinical trials in juvenile idiopathic arthritis

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There have been unprecedented advances in the treatments and outcomes reported for patients living with juvenile idiopathic arthritis (JIA) over the last 20 years. The future direction of care with multinational collaborations (Paediatric Rheumatology International Trials Organisation (PRINTO), Pediatric Rheumatology Collaborative Study Group (PRCSG), Childhood Arthritis and Rheumatology Research Alliance) and advances in precision medicine will undoubtedly continue to revolutionise our approach to diagnosis, treatment and perhaps ultimately cure of JIA. In Annals of the Rheumatic Diseases, Brunner et al report on the use of subcutaneous golimumab for children with active polyarticular course JIA.3 This trial, no doubt associated with immense direct and indirect costs, produced negative results, as it did not achieve its primary end point. Despite this, there is widespread international opinion that golimumab, like other tumour necrosis factor (TNF) inhibitors, is effective and should be added to the therapeutic armamentarium for children with JIA. We must reflect on this outcome as we consider further studies with new agents in the treatment of children with JIA.

To date, three trials of anti-TNF agents (etanercept, infliximab and adalimumab),2–4 one of a selective T cell costimulation modulator (abatacept),5 and an interleukin-6 receptor inhibitor6 (tocilizumab) have shown efficacy and safety in the treatment of polyarticular course JIA in spite of the fact that primary end point of efficacy was not met in the infliximab trial. Amarillo et al7 published a meta-analysis of randomised withdrawal trials which evaluated the five separate trials (abatacept,5 adalimumab,8 anakinra,9 etanercept10 and tocilizumab6) all versus placebo. There were no statistical differences among biological agents for efficacy or safety. The parallel design infliximab trial published in 2007 failed to meet the primary efficacy end point of American College of Rheumatology Pediatric 30 Criteria (ACRPed30) at week 14 of infliximab (3 mg/kg) versus placebo.3 Several factors including inadequate infliximab dosing, too brief placebo treatment phase and higher-than-expected placebo-response rate may have contributed to these negative results. Concerns regarding this study, some of which we raise again 10 years later, were addressed in an accompanying editorial.11 Subsequently, infliximab monotherapy was shown to be effective in the aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA trial),12 a randomised open-label trial that compared methotrexate, methotrexate/sulfasalazine/hydroxychloroquine (COMBO) and infliximab (3–5 mg/kg) in disease-modifying antirheumatic drug-naïve patients. At week 54, ACRPed75 was achieved in 100% on infliximab, 65% on COMBO and 50% on methotrexate monotherapy, p<0.0001. Furthermore, patients on infliximab remained in a state of inactive disease for a longer duration (6 months) than the other two treatment arms (3 months for COMBO and 1 month for methotrexate). Despite the initial negative trial, infliximab continues to be used in clinical practice with effectiveness reported similar to the other biological agents.13

There are inherent challenges in the study of treatment efficacy in children and in particular concerning rare diseases such as JIA.11 14–16 There are requirements from the medical community, pharmaceutical industry and regulatory agencies that have an ethical responsibility to design, conduct and report on high-quality studies of medicines in children. To minimise the number of children exposed to placebo while providing adequate recruitment, the three-part placebo-controlled, double-blind, randomised withdrawal design17 has been used in several trials in patients with JIA. This trial design tends to overestimate the effect of the trial agent, as only those who have an initial response proceed to the blinded withdrawal phase. Theoretically, this design should be limited to drugs with short half-lives that will not lead to carry-over effects; otherwise the time of the second phase would need to be increased, thus negating the benefit of this trial design.

In the current golimumab study, members of PRINTO and PRCSG report on the use of golimumab in polyarticular course JIA resistant to treatment with methotrexate.1 The study involved 33 sites in 12 countries for a total enrolment of 173 patients. Similar to the etanercept, adalimumab, abatacept and tocilizumab trials, the study was a randomised withdrawal trial with the primary outcome defined as JIA flares in the withdrawal phase. Secondary outcomes included ACRPed50/70/90 responses, clinical remission, pharmacokinetics and safety. In the open-label phase, 89%/79.2%/65.9%/36.4% demonstrated an ACRPed30/50/70/90 response. At the end of phase II (week 48) the primary end point was not met (JIA flares, golimumab vs placebo: 32/78=41% vs 36/76=47%; p=0.41).

It is important to consider the reasons why this trial might not have met its primary end point. One can postulate on the possible factors contributing to the negative results. (1) The long half-life of golimumab could have led to carry-over effects in the randomised withdrawal phase. (2) Disease duration at time of initiation of golimumab as well as duration and dosing of methotrexate may have had a differential impact on response to therapy.12 18 The eligibility criteria specified disease duration of at least 6 months but disease duration at baseline was not collected; the proportion of patients on a dose of 15 mg/m² subcutaneous methotrexate was not provided. (3) The presence of neutralising antibodies could have had an effect on efficacy (the number of patients with high titre neutralising antibodies was small (n=8) in this study precluding definitive assessment of the clinical impact). The other main biological trials2–6 similarly report low prevalence and generally low titre neutralising antibodies, but there are issues with the timing of testing, reliability of the assays and generalisability of the results. The prevalence and potential clinical significance of antidrug antibodies in primary and secondary treatment failure to biological agents in paediatric rheumatology warrants further investigation.

There are no doubt differences in the pathogenesis of rheumatoid arthritis (RA) and JIA, at minimum as evidenced by the absence of circulating autoantibodies (rheumatoid factor and anti-cyclic-citrullinated peptide (CCP)) in most cases as well...
as the presence of chronic anterior uveitis; however, there has yet to be a biological agent that has proven to be ineffective for use in JIA once its effect has been demonstrated in RA. Similarly, biological agents found to be effective in the adult spondyloarthropathies have been successful in the paediatric population with enthesitis-related arthritis,\(^2\) a forerunner to spondyloarthropathy in later years. Furthermore, biological agents effective in systemic JIA have been used successfully in adult-onset Still’s disease, likely the same disease differentiated essentially by the age of onset.

As highlighted, there are many challenges in conducting typical randomised controlled trials in paediatric patients including ethics, acceptability, difficulty in recruiting an adequate sample size, rarity of disease and standardisation (age, outcome measures, selective reporting) and alternate trial designs are not without challenges. It may be time to rethink the regulatory approach to approvals of biological agents that have been documented to be effective in the adult population. At a minimum, perhaps approval of a new biological agent for non-systemic polyarticular course JIA (that already has proven efficacy in RA) should only require paediatric trials of pharmacokinetic and safety to save the time and expense of a clinical trial only to have it fail. Alternatively, perhaps, as shown in systemic JIA,\(^2\) the randomised placebo-controlled trial with early escape should again be considered. Either approach will save significant resources and allow patients to get the treatment they need in a more expeditious way.

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