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Editorial

Real-world or clinical trial data for treatment of children with rheumatic diseases?

This editorial refers to *Efficacy and safety of tocilizumab in a real-life observational cohort of patients with polyarticular juvenile idiopathic arthritis* by Grönlund *et al.*, doi:10.1093/rheumatology/kez291

The standard of care for the management of children with JIA has moved towards a step-by-step escalation, with early immunosuppressive therapy to achieve remission. Biologics have markedly improved disease control in JIA, and in many centres anti-TNF-α therapies represent the first-line treatment in children refractory to MTX. However, a subset of children, overall ∼30% of JIA patients, fail to respond to TNF-α blockers or are unable to tolerate these therapies and may therefore benefit from switching to another drug. In this clinical setting, the availability of several different molecules provides the chance to offer alternative therapeutic options to achieve remission on medication and, eventually, even off medication. Targeting IL-6 blockade represents a window of opportunity either for those who are anti-TNF-α non-responders or as the first-line biological agent soon after the DMARD failure in polyarticular JIA [1, 2].

Randomized clinical trials (RCTs) remain the best source of robust evidence; however, data from real-world settings may provide valuable information too. In a multicentre randomized controlled withdrawal trial (CHERISH), 188 patients with polyarticular JIA received open label tocilizumab (TCZ) for a period of 16 weeks, after which these patients received either placebo ($n = 81$) or TCZ ($n = 82$) for a further 24 weeks. In children with polyarticular JIA, TCZ resulted in significant improvement, maintained over time [3]. TCZ has also been shown to be efficacious in severe, persistent systemic JIA [4].

These two studies provided evidence of the efficacy and safety, at least for the time period of the study, for the use of TCZ in JIA. If RCTs are designed and performed with stringent methodological rigor, they provide replicable data and firm conclusions, limiting the risk of bias or misinterpretation [5, 6]. Although RCTs provide one of the best sources of evidence for our clinical practice, there are limitations to these data. In the quest for homogeneous populations and the need for easily interpretable data, the stringent inclusion/exclusion criteria provide a controlled subset of the population that does not always mirror the overall population attending our paediatric rheumatology outpatient clinic. For example, owing to the inclusion criteria, children who do not have five or more active joints are ineligible for the CHERISH trial; therefore, data regarding the potential use of TCZ in JIA children with fewer than five active joints are not available. Nonetheless, in clinical practice these children may be significantly debilitated and are also likely to benefit from TCZ use. The withdrawal design used in CHERISH and other paediatric trials provided the evidence base for therapies in children without subjecting children with polyarthritis to placebo at the outset. However, a major limitation of the withdrawal design is that it does not mirror routine clinical care, because treatment would not usually be discontinued after 3–4 months of initiating biological treatments. Therefore, some children have their effective medication removed prematurely. Given that there are an increasing number of potential new therapies that are ready to be trialled in children, the most pressing need is a comparison with the existing standard of care rather than placebo [7]. Also, trials of new agents with long half-life (e.g. golimumab) in withdrawal design studies may not meet the primary end point owing to patients entering clinical trials with milder disease. We acknowledge that large sample sizes needed for comparative trials make conventional comparative study designs in a disease such as JIA less feasible [8]. However, there are now examples of studies with active reference arms using Bayesian methodology, which might be a way forward [9].

Data from real-world studies reflects and represents our typical population; therefore, data from real-world outcomes can help in directing our routine clinical practice. Observational studies usually mirror what is done in routine clinical care.

In the present issue of *Rheumatology*, Grönlund *et al.* [10] report outcomes of TCZ use in clinical practice of treating poly-JIA, adding significant data regarding the use of TCZ in real-world clinical practice. Of note, they report high rates of effectiveness in children with JIA, even in those with longstanding and treatment-resistant disease, over 24 months of analysis. In their study, TCZ proved useful even in patients whose JIA had previously been refractory to other biological therapies. The poly-JIA population included in the study was more likely to reflect the wider poly-JIA population, in that they were children who had received at least two previous biological treatments. The high percentage of patients with low disease activity at 24 months of treatment adds significant value to RCT results obtained over a shorter time period and by a withdrawal design.

Conversely, one drawback with this paper is that the authors do not stratify and correct the principal outcome

for the impact of covariables (i.e. disease duration, number and type of previously used therapies), which might impact on the final effect size of the clinical outcome. Given that the inclusion criteria were not so stringent and there was no rigid study design, the real-world data might be liable to misinterpretation [11]. There are epidemiological approaches that might enable the weighting of the single effect of each variable of interest. Thus, the proper interpretation of data from real-world studies necessitates the analysis of multiple variables that might influence the total effect size [11]. All these potential variables have to be taken into account, in a comprehensive manner, before drawing conclusions from observational study results. In RCTs, we obtain results from an a priori study design; whereas in real-world studies, before running the statistical evaluation, the a priori analysis of potential influencers of the biological phenomenon of interest should be considered. Without this rigour, the potential to obtain misleading results from real-world studies may be high.

In this clinical setting, national rather than multinational registries seem to offer the highest chance of ensuring good-quality data. Potential limitations associated with the use of registries may be managed using appropriate statistical corrections. A registry, coupled with good epidemiological expertise, can significantly enhance the quality of observational real-world studies. Additionally a registry can provide longitudinal data on safety in addition to efficacy [12], although RCTs usually have a long-term extension study of participants for safety reasons.

Both RCT and real-world data are complementary. What will be needed in the future are clinical trials to address the key questions that parents and clinicians face when making decisions. This might entail studies that compare new agents with existing therapies rather than placebo-controlled or withdrawal designs. These studies, coupled with real-world data and registries for long-term safety, will help to move the evidence-based care of children with rheumatic diseases forwards.

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