Blinded by lack of evidence

Clinical trials in JIA-associated uveitis


A significant proportion of children with JIA-associated uveitis continue to develop considerable visual complications secondary to uveitis despite progress in establishing screening programmes in most countries [1–4]. The question that remains unanswered is why is there a reluctance to immunosuppress patients with active and potentially sight-threatening uveitis? The answer may be a lack of robust evidence to support this approach, as there are insufficient patients with active joint disease with JIA [5]. For example, the data show that MTX is effective in two-thirds of children with active arthritis as a disease-modifying agent [6]. Additionally, advances in biotechnology and drug development provide early evidence for the efficacy of biologic therapies in the treatment of arthritis in children with JIA. Should we be doing more for our patients with uveitis [5]? Perhaps the lack of robust evidence for eye diseases, the systemic safety concerns of biologic therapies when used for eye disease and reluctance on behalf of ophthalmologists to initiate are potential reasons for the delay in adoption of systemic immunosuppressive therapy?

Simonini et al.’s [7] work in this issue of Rheumatology is important and timely in helping us address these issues and provide an increased level of evidence for the use of MTX in childhood uveitis. In their meta-analysis and data synthesis of nine published studies, the authors present the case for efficacy of MTX in childhood chronic uveitis [7]. This is admirable, particularly as all nine papers chosen for this meta-analysis are observational or retrospective studies, as there are no controlled trials of DMARDs in childhood-onset uveitis. The future, therefore, is now to sway the balance and convince clinicians to treat early. Also, what cannot be ignored is the potential harm of current therapy. For example, 1–3 drops/day of topical steroid eye drops, in an attempt to control ocular inflammation, can increase the risk of cataracts and raise intraocular pressure [8]. The current data, more than ever before, support the need for systemic treatment of uveitis [9], especially as there is some evidence to show that early treatment with MTX may reduce the risk of cataract surgery in children [10, 11].

Nevertheless, there remain unanswered questions on issues of how to optimize MTX therapy. The MTX dose used in the studies analysed varied widely from 7.5 to 30 mg/m². Although evidence supports efficacy, Simonini et al.’s meta-analysis also reveals significant caveats. For instance, the lack of clarity with the use of concomitant topical steroid makes it difficult to assess the overall benefit for the patient. Despite this, the meta-analysis does show that MTX is effective in almost two-thirds of children with uveitis, but both the appropriate dose for treatment of uveitis and the duration of therapy needs to be defined. The latter is of particular importance, as the evidence shows that early withdrawal of MTX after remission is associated with higher risk of relapse [12].

The data by Simonini et al. [7] are supported by other large studies such as the American Systemic Immunosuppressive Therapy for Eye (SITE) Disease Cohort Study [13]. This study shows that in a heterogeneous mix of uveitic disorders in adults and children, MTX showed a 60% efficacy to maintain control of inflammation and reduce steroid requirement. Importantly, the authors commented that patients below 18 years of age were less likely to respond fully. Even with the available evidence, it is unlikely that a head-to-head or comparative placebo-controlled trial with MTX will be done in the future. So where do we go in the future?

Arguably, the need of the hour is to look at whether newer biologic therapies in children with uveitis refractory to MTX (on a standardized dose regime) enable remission of disease [5]. Unfortunately, to date, most of the trials of biologic therapies in JIA have excluded children with active uveitis from being entered into the trials, and so we are reliant on evidence from small case series. Greater collaboration between ophthalmologists and rheumatologists will help studies, especially randomized controlled trials, and provide an evidence base for newer agents in children with uveitis. It is important for regulatory bodies such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) working closely with the pharmaceutical industry, to continue to ensure that trials of biologic agents are undertaken for orphan indications such as uveitis in children. With their support, efforts such as the Sycamore trial—a randomized controlled trial looking at the efficacy of adalimumab in JIA-associated uveitis (http://www.controlled-trials.com/ISRCTN10065623)—can be developed to avoid significant yet potentially preventable morbidity from uveitis in children.

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References