Real-World Outcomes of Biologic Therapy for Juvenile Idiopathic Arthritis Associated Uveitis

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ABSTRACT

Purpose: We aim to report the outcomes and complications of patients with uveitis from Juvenile Idiopathic Arthritis (JIA) treated with biologic therapy.

Materials and Methods: All patients who underwent treatment with biologic therapy for uveitis in the context of JIA between 2016 and 2017, followed in the Uveitis Department in Hospital de Santa Maria, were retrospectively included in the study. Patient medical records were analyzed retrospectively and clinical outcome and complications were registered.

Results: Nine patients (7 females, 2 males, 18 eyes) were included in the study. The mean age of JIA diagnosis was 6.6 years (±4,5) and the mean age of uveitis diagnosis was 7.9 years (±3,0). Six patients were being treated with adalimumab (ADA), 2 with Infliximab (IFX) and 1 with Tocilizumab (TCZ), and of them 8 (88,9%) were treated successfully for uveitis. The resolution of anterior chamber inflammation was obtained with a mean interval of 2 months for ADA and 3 months for IFX. Before starting biologic therapy 33,3% (n=3) patients were on oral steroids, 55,6% (n=5) were doing methotrexate and 11,1% (n=1) was doing cyclosporine. After biological treatment, no patient was on oral steroids. Regarding adverse effects, there are records of one reaction to infusion during the treatment with IFX and liver enzymes derangement with ADA, that resulted in the switch of therapy respectively to ADA and IFX.

Conclusion: In this small cohort, ADA, IFX and TCZ showed to be effective and relatively safe for treatment of JIA-associated uveitis.

Keywords: Biologic Therapy, Juvenile Idiopathic Arthritis, Uveitis

INTRODUCTION

JIA is the commonest rheumatic disease in children and JIA-associated uveitis (JIA-U) its most frequent extra-articular manifestation. Of all cases of uveitis, approximately 6 out of 100 occur in children, with up to 80% of these associated with JIA, making this disease the most commonly identified cause of uveitis in children. The uveitis is potentially sight-threatening and thus carries a considerable risk of morbidity with associated reduction in quality of life. The aim of treatment is to achieve complete elimination of active inflammation.[1]

The first-line treatment for both acute and chronic anterior uveitis is topical steroids.[2] The primary indication for systemic immunosuppression with one of the disease-modifying antirheumatic drugs (DMARDs) is failure of adequate control of inflammation after 3 months of topical treatment, particularly with >3 drops daily.[2] Methotrexate remains the first second-line therapy after topical steroids and is the most commonly prescribed immunosuppressive therapy in paediatric uveitis.[3] However, with topical steroids up to 48% children do not achieve control of inflammation and 20% experience adverse events.[4,5]

Biologic therapy is a novel treatment modality with the aim of regulate the inflammatory process and has been successfully used in the treatment of several immune-mediated rheumatic disease. Their mechanism of action consists in specific targeted suppression of immune effectors response that damage tissue. The term 'biologic' or 'biological' was coined because these drugs are usually proteins (and frequently antibodies) generated within a biological system and not by chemical synthesis.[6]

Over the past decade, randomised controlled trials (RCTs) of biologic agents have demonstrated their efficacy in controlling joint disease in JIA.[4] The same drugs have also been used in the treatment of associated uveitis. Use of infliximab (IFX) in the management of refractory paediatric uveitis was first reported in 2005.[7] Adalimumab (ADA) was licensed in Europe for adult and paediatric non-infectious uveitis in 2016 and 2017 respectively following successful outcome of randomised controlled trials (RCTs).[8,9]

Yet, in the era of biologic treatment, there is a paucity of data on longer term outcomes of paediatric uveitis (including JIA-U).[2]

With this retrospective study we aim to report the real--world outcomes and complications of patients with uveitis from JIA treated with biologic therapy attending in a tertiary hospital in Portugal.

MATERIALS AND METHODS

Patient identification

Clinical notes were reviewed to identify all patients with JIA-U. Children were included if they had been managed in Hospital de Santa Maria, followed in the Uveitis Department, and treated with biologic therapy due to uveitis only in the context of JIA, between 2016 and 2017.

Patient clinical notes were analyzed retrospectively and clinical outcome and complications were registered.

Data collection

Data was collected retrospectively and clinical outcome and complications were registered. Demographic data included age at diagnosis and gender. Clinical uveitis details included anatomical location using Standardization of Uveitis Nomenclature (SUN) criteria[10] and structural complications. Pharmacological and surgical treatments were documented. Visual acuity was recorded in logMAR.

RESULTS

Nine patients (7 females, 2 males) were included in the study. The mean age of JIA diagnosis was 6.6 years (standard deviation [SD], 4.5) and the mean age of uveitis diagnosis was 7.9 years (SD 3.0). Oligoarticular arthritis was the JIA subtype present in 7 cases (77.8%) and polyarticular arthritis subtype in 2 cases (22.2%). Only 2 patients were negative for anti-nuclear antibody.

Bilateral anterior uveitis was the most common form of uveitis occurring in all patients. Two patients had also intermediate uveitis. As uveitis complications, 3 patients had secondary glaucoma, and 5 eyes had cataract and band keratopathy. Optic papillitis and macular edema were also observed in 1 patient.

Regarding VA, the eyes with only anterior uveitis presented with better VA before starting the biological treatment, with a mean VA of 0,05 logMAR. At the last observation there was an improvement of mean VA in theses eyes to 0,01 logMAR. The eyes that presented at least one complication (cataract, vitrectomy, glaucoma,

papillitis) presented worse VA before starting the biological treatment, with a mean VA of 0,56 logMAR. In addition, they also showed a decrease in VA during the follow-up, with a mean of visual at the last observation of 0.82 logMAR.

Surgical treatment was required in 4 patients and in all cases one eye received at least 2 surgical procedures. Cataract extraction was the most common procedure, performed in 5 eyes. Three eyes were submitted to glaucoma surgery: one had trabeculectomy, one had XEN implantation and another one had surgical iridectomy. Vitrectomy was performed in 2 eyes. Vitrectomy indication data for 1 eye was not available because this patient underwent surgery prior to follow-up at this hospital, and the other vitrectomized eye was submitted to this surgical procedure because of vitreal debris.

The first line systemic immunosuppressive agent for all children was methotrexate. The patients were treated with biologic if there was no remission with the first line therapy. Mean follow-up time of patients after initiating the actual biologic was 22 months, ranged from 3 to 60 months.

Before starting biologic therapy, 33,3% (n=3) patients were on oral steroids, 55,6% (n=5) were doing methotrexate and 11,1% (n=1) was doing cyclosporine. Patients that were on oral steroids had previously been on MTX but had to stop due to side effects. At the baseline, 4 patients were treated with IFX, 2 with ADA and 3 with Etanercept (ETA). The three patients who were being treated with ETA for articular disease, changed to ADA (n=2) or IFX (n=1) when uveitis was diagnosed for the first time. Three patients switched therapy from IFX to ADA because of primary non-efficacy (n=1), loss of efficacy after 10 years of treatment (n=1) or because of an adverse effect to IFX (n=1). Only one patient switched from ADA to IFX because of absence of primary response. One patient with poliarticular JIA did not respond in what concerns to articular disease to neither ADA or IFX, but had a good clinical response to TCZ and conventional immunossupression with cyclosporine A, besides of initial good response of the uveitis to ADA.

During the year of 2017, 6 patients were being treated with ADA, 2 with IFX and 1 with TCZ, and of them 8 (88,9%) were treated successfully for uveitis. The only patient who maintained uveitis after starting biological treatment, even under topical steroids, was the patient with the lowest follow-up time.

The resolution of anterior chamber inflammation was obtained with a mean interval of 2 months for ADA and 3 months for IFX. All patients were treated with topical steroids (less than 3 drops of topical prednisolone a day). At the time of data collection, no patient was on oral steroids, 55.6% (n=5) were doing methotrexate and 11,1% (n=1) was doing cyclosporine. It was possible to reduce (n=5) or stop (n=4) topical steroids in all patients.

Regarding adverse effects, there are records of one reaction to infusion during the treatment with IFX and liver enzymes derangement with ADA, that resulted in the switch of therapy respectively to ADA and IFX.

During the treatment with biologics, 2 patients had to stop the treatment because of infectious intercurrences. In one of these, uveitis recurrence was observed after 14 weeks in the absence of treatment, but new remission was observed after resumption of treatment.

DISCUSSION

In a step-by-step approach, topical and/or systemic steroids and/or DMARDs are often needed to achieve inactivity of articular and ocular inflammation.[11,3]

If ocular inflammation inactivity is not achieved with synthetic DMARD (mainly methotrexate), tumor necrosis factor inhibitors (anti-TNF) are considered as treatment options in JIA-U; with a strong body of evidence supporting their efficacy and safety.[12,13,14] Among the monoclonal antibody biologic agents that suppress inflammation by binding proinflammatory cytokines, the most effective for ocular inflammation are the anti-TNF IFX and ADA. They can be used alone or in combination with classic immunomodulatory therapy.[15]

Currently, ADA is the only approved anti-TNF to treat JIA-U; a pooled analysis of results from previous observational studies showed about 87% of children responding (compared with 72% for infliximab and 33% for etanercept).[4] ADA was licensed for paediatric non-infectious uveitis in 2017 following successful outcome of the SYCAMORE Trial.[9] This trial supported the efficacy of ADA therapy in combination with methotrexate as an effective therapy in children and adolescents with refractory to conventional immunosuppressive therapy. But evidence for biologic treatments other than ADA remains limited in childhood uveitis.[1]

For severe uveitis refractory to anti-TNF, further treatment options are required. Use of TCZ, a fully humanised anti-IL6R antibody, for treatment of JIA-U was previously reported only in small case series.[16,17] Within the last two years, two larger, multi-centre, retrospective cohort studies including 17 and 25 patients have been published,[18,19] showing that TCZ appears to be a useful therapy in severe refractory JIA-U.

In our small cohort, uveitis in all patients responded to anti-TNF, but one patient with poliarticular JIA swiched ADA therapy to TCZ to control articular diasease. The resolution of anterior chamber inflammation was observed in 88,9% of the patients with a satisfied mean interval of response. The improvement of VA in patients with no underlying ocular complications is also a positive indicator of treatment success.

The recent publication of the SYCAMORE Trial,[9] on the other hand, reported that patients who received ADA had a much higher incidence of adverse events and serious adverse events than those who received placebo. In our small cohort, the majority of complications were managed with the biological therapy switch.

As a retrospective study we acknowledge certain limitations to the study. The duration of follow up within the patient cohort was unequal in some cases. The small sample is another limitation of this study.

There is increasing evidence for the early introduction of systemic immunosuppressive therapies to reduce topical and systemic use of steroids. The era of biologic therapy has brought improvements in visual outcomes for children with uveitis that may also result from improved clinical practice, like multidisciplinary teams that carry out a closing monitoring of affected children, managing and adjusting the therapy early in the course of the disease. This includes audited JIA-U screening standards,[20] even for children without ocular symptoms. In our Hospital, the establishment of combined rheumatology and uveitis clinic has been crucial in providing timely and effective monitoring and management for children with uveitis.

Uncertainties remain on the optimum duration of systemic treatments for children with uveitis as well as the visual outcomes of those children with uveitis moving on to adulthood.[1] Nonetheless, biologic agents are expensive and carry an increased risk of infection and other side effects[21] and so their use needs to be balanced against the potential benefits in reducing sight loss.

CONCLUSION

In this small cohort, ADA, IFX and TCZ showed to be effective for treatment of JIA-U and for visual outcomes of non complicated-uveitis non responsive to conventional therapies. Although some complications have been recorded, they were managed successfully with the biological drug switch or temporary withdrawal of therapy.

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