ISSN: 2475-6296

Research Article

Journal of Clinical & Experimental Immunology

Patience and Time, they will do it all

Arjun Rangaraj, Archana Pradeep, Kishore Warrier, Samundeeswari Deepak, Vishal Paisal and Satyapal Rangaraj

Nottingham University Hospitals NHS Trust, Nottingham, UK

***Corresponding author**
Arjun Rangaraj, Nottingham University Hospitals NHS Trust, Nottingham, UK

Submitted: 02 Mar 2022; **Accepted**: 10 Mar 2022; **Published**: 21 Mar 2022

Citation: *Arjun Rangaraj, Archana Pradeep, Kishore Warrier, Samundeeswari Deepak, Vishal Paisal, et al. (2022) Patience and Time, they will do it all. J Clin Exp Immunol, 7(1): 441-442.*

Background and Introduction:

Uveitis, intraocular inflammation of Uvea, is a major cause of blindness worldwide [1]. Depending on the site of inflammation, it is classified as anterior, intermediate, and posterior or pan uveitis, with anterior uveitis being the most common [2]. Children and Young People (CYP) may account for 33% of Uveitis [3]. The commonest associations with Uveitis in CYP are Juvenile Idiopathic Arthritis (JIA) and parasitic infections; 25% are idiopathic in nature [3, 4].

Due to its common association with JIA, and need to exclude other causes of Uveitis, paediatric rheumatologists are often involved in the initial and subsequent management of Uveitis in CYP alongside the ophthalmologists [5]. Initial treatment of Idiopathic Uveitis (IU), involves steroids, often topical or less commonly systemic [6]. For persistent IU, immunomodulation with disease modifying antirheumatic drugs (DMARDs) are cornerstones of treatment. Paediatric rheumatologists usually lead on prescribing and monitoring DMARDS as they have the expertise in using these medications. The first line DMARD is often Methotrexate, and second line biological DMARDs (bDMARDs) are often anti-Tumour Necrosis Factor alpha drugs such as Adalimumab or Infliximab [7]. These are similar to treatments in CYP with JIA.

In JIA after achieving a period of remission in disease activity, the DMARDs are discontinued to assess continued need for medication [7]. Generally, this period of drug induced remission is at least two years, before a trial off medication is considered [8]. In JIA, the remission rate after discontinuation of DMARDs is nearly 50% with the other half relapsing within one year7 [9].

The recommended time period for trial off DMARDs in IU is 2 years of drug induced remission 11, in line with JIA. There is limited evidence on number of CYP with IU who relapse or maintain remission after this time period. Herein, we report a retrospective review of CYP who were on DMARDs and if they achieved drug free remission of disease activity after a trial off DMARDs [10].

Methods

All children and young people (CYP) < 18 years of age from a tertiary Paediatric Rheumatology Unit, who are either newly referred for management of IU from the Ophthalmology department or currently under active management, over a 5 year period. Uveitis associated with other causes such as JIA and parasitic infections were excluded. Notes were reviewed retrospectively, and longitudinal data including presentation of symptoms, inflammatory cells present in anterior chamber, commencement of treatment with DMARDs, subsequent progress, flare up/ control of Uveitis, addition of second line bDMARDs to treatment, remission achieved, and period of remission was extracted from the electronic patient notes. The end point of the 5 year period was chosen to be 3 years prior to data collection, such that CYP who are studied had a minimum period of 2 years of treatment.

Results

A total of 9 new CYP with IU were referred to the Paediatric Rheumatology Unit for assessment and further management over the 5 year period. There were 14 CYP actively managed during the same time period, making it a total of 23 CYP managed during the 5 year period. All had inflammatory cells in the anterior chamber at presentation.

The median age was 9 years (range: 2-16).
Male to female ratio was 9:14.

Medication were still being continued on 21/23 patients towards the end of the 5 year period. The median time period of being treated on DMARDs was 82 months (range: 27-163).

Medication were discontinued in 2/23 patients over the 5 year period. One patient achieved remission and discontinued DMARD after 36 months. In this patient, Uveitis was preceded by meningococcal meningitis, and it was suspected that the Uveitis was triggered by infection rather than being IU. Diagnosis was changed retrospectively in another patient from IU to infection related pan uveitis, proven by biopsy, and treatment with DMARD was discontinued at 17 months.

The initial choice of DMARD was Methotrexate and all 23 CYP were commenced on this. The median time between referral to commencement of DMARD was 6 months (range: 0-14). 9/21 CYP achieved drug induced remission for a minimum of 2 year period, but unsuccessfully trailed off and recommenced on DMARDs after a median of 4 months (range: 1-8).

A second line DMARD/ bDMARD was commenced in 14/23 CYP. Of these, Adalimumab was commenced in 9 CYP, Infliximab in 4 CYP and Mycophenolate Mofetil (MMF) in 1 CYP.

A third line biological agent was commenced in 2/14 CYP and of these one was Adalimumab and the other was Infliximab.

Discussion

Our study showed that all CYP with IU continued to remain on treatment over the 5 year period. Though we had expected a significant proportion of CYP with IU to have stayed on treatment, it was surprising to see all CYP to have continued on treatment during this period. Though there were no comparable data, one study which included all ages and causes except infection, showed one third went into remission at 5 years and nearly half at 10 years [11, 12]. The same study found that younger age groups had more severe course and had lower incidence of remission.

The weakness of our study is its retrospective nature and combining the new and the existing CYP on treatment. Patients with longer follow-up at tertiary centres tend to be those with more severe disease, which could increase the prevalence of complications and poor outcomes; the existing CYP on treatment may belong to this group.

Strengths of our study include availability of data during the entire study period, all care being provided at the same tertiary centre, the large patient population. Our results show that CYP may take a particularly longer time to achieve remission. This may provide a basis for counselling and educating patients and parents regarding the likely course and duration of treatment, as well as providing guidance for clinical management.

It is possible that the current recommendation of having a trial off medication in 2 years, was extrapolated from other associated conditions such as JIA. Our study shows that this is often a failure, possibly causing considerable distress to families and children, and poorer disease control. It is probable that this group will need much more patience and time for the disease to resolve [13].

CYP and family will be better prepared if the correct information is given during counselling at commencement of DMARDs. Further studies on bigger population and longer term is prudent to determine exactly how many CYP with IU go into remission and the duration of the disease. Once a better understanding of duration is established, the ideal time for trialling off DMARDs can be determined.

References

1. Suttorp-Schulten, M. S., & Rothova, A. (1996). The possible impact of uveitis in blindness: a literature survey. The British journal of ophthalmology, 80(9), 844.
2. Chang, J. H. M., & Wakefield, D. (2002). Uveitis: a global perspective. Ocular immunology and inflammation, 10(4), 263-279.
3. BenEzra, D., Cohen, E., & Maftzir, G. (2005). Uveitis in children and adolescents. British journal of ophthalmology, 89(4), 444-448.
4. Smith, J. A., Mackensen, F., Sen, H. N., Leigh, J. F., Watkins, A. S., Pyatetsky, D., ... & Goldstein, D. A. (2009). Epidemiology and course of disease in childhood uveitis. Ophthalmology, 116(8), 1544-1551.
5. Pooja Bhat, D. G., & Goldstein, D. A. (2019). Pediatric anterior uveitis.
6. Sood, A. B., & Angeles-Han, S. T. (2017). An update on treatment of pediatric chronic non-infectious uveitis. Current treatment options in rheumatology, 3(1), 1-16.
7. Gottlieb, B. S., Keenan, G. F., Lu, T., & Ilowite, N. T. (1997). Discontinuation of methotrexate treatment in juvenile rheumatoid arthritis. Pediatrics, 100(6), 994-997.
8. NRAS (2021) Methotrexate. JIA at NRAS https://jia.org.uk/resource/methotrexate.
9. Ravelli, A., Viola, S., Ramenghi, B., Di Fuccia, G., Ruperto, N., Zonta, L., & Martini, A. (1995). Evaluation of response to methotrexate by a functional index in juvenile chronic arthritis. Clinical rheumatology, 14(3), 322-326.
10. Foster, C. S., Kothari, S., Anesi, S. D., Vitale, A. T., Chu, D., Metzinger, J. L., & Cerón, O. (2016). The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. survey of ophthalmology, 61(1), 1-17.
11. Tripathy, K (2021) Immunomodulatory Therapy (IMT) for Ocular Inflammation. American Acaedemy of Ophthalmology https://eyewiki.org/Immunomodulatory_Therapy_(IMT)_for_Ocular_Inflammation#Duration_of_the_IMT.
12. Sobrin, L., Pistilli, M., Dreger, K., Kothari, S., Khachatryan, N., Artornsombudh, P., ... & Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study Research Group. (2020). Factors predictive of remission of chronic anterior uveitis. Ophthalmology, 127(6), 826-834.
13. Tolstoy, L. (2016). War and peace. Lulu. com.