Adalimumab in juvenile-idiopathic arthritis-associated uveitis (JIA-U): 5-year follow-up of the Bristol participants of the SYCAMORE trial.

Horton S[1], Jones AP[2] , Guly CM[1], Hardwick B[2], Beresford MW[3, 4], Lee RWJ[1,5, 6], Dick AD[1,5, 6], Ramanan AV[5, 7]

[1] Bristol Eye Hospital, University Hospitals Bristol NHS Foundation Trust, Bristol, UK, [2] Clinical Trials Research Centre, Department of Biostatistics, University of Liverpool, Liverpool, UK, [3] Department of Women's and Children's Health, Institute of Translational Medicine, University of Liverpool, Liverpool, UK, [4] Department of Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust, Liverpool, UK, [5] University of Bristol, Bristol, UK, [6] National Institute of Health Research and Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK, [7] Department of Paediatric Rheumatology, University Hospital Bristol NHS Foundation Trust, Bristol, UK

Corresponding author

Professor A. V. Ramanan

Dept. of Paediatric Rheumatology, Bristol Royal Hospital for Children

Bristol UK BS6 6BT

Email – avramanan@hotmail.com

Introduction

Juvenile-idiopathic arthritis-associated uveitis (JIA-U) occurs in 13-24% of patients with JIA within seven years of diagnosis of arthritis and is the most common cause of uveitis in children and young people [1,2,3]. The disease largely follows a chronic, indolent course with a high risk of complications resulting in visual impairment, including posterior synechiae, band keratopathy, glaucoma and cataract and has a significant impact on the quality of life and emotional well-being of patients [4,5,6,7]. JIA-U was traditionally managed with topical steroids, but early use of methotrexate is now highly recommended to control uveitis and reduces the risk of steroid-induced cataract and glaucoma [8,9]. However, despite early intervention, methotrexate may not fully control uveitis and some children develop intolerable side effects [10].

The SYCAMORE trial, a randomized, multi-center (17 UK centers), placebo-controlled, double-blind trial, showed clear therapeutic benefit of adalimumab and has led to licensing of adalimumab for JIA-U in Europe [11,12]. All 90 participants recruited to the trial had disease that was refractory to topical or systemic steroids and methotrexate. Addition of adalimumab decreased the hazard of treatment failure by approximately 75% as compared to placebo (hazard ratio 0.25, 95% confidence interval [CI], 0.12 to 0.49; P<0.0001 by the log-rank test), defined according to a multicomponent intraocular inflammation score based on the Standardization of Uveitis Nomenclature (SUN) criteria [13]. Trial participants were followed-up for 6 months after withdrawal of the investigational medicinal product (IMP) (adalimumab or placebo).

This study reports on outcomes of participants from a single center and major recruiting site to SYCAMORE. The aim was to evidence longer-term outcomes including visual acuity and safety as well as disease activity and document the time to flare after stopping adalimumab.

Methods

All participants of the SYCAMORE trial recruited to the Bristol Eye Hospital were identified through the local Research and Development Department. A retrospective audit of data was approved by the local research board. Records were reviewed by the first author for up to 5 years from the study randomization date until 31st July 2017, at intervals as close to 3-monthly as routine clinic reviews would allow. Data extracted from clinical records and recorded on a pre-specified data proforma included visual acuity in LogMAR units, disease activity according to SUN grading, treatment, ocular complications and adverse events. Active uveitis (flare) was defined in this study as SUN grading 1+ or above of anterior chamber activity in either eye recorded on at least one visit.

In the SYCAMORE trial (full SYCAMORE trial methodology is outlined in the original article [10]) all participants were randomized to treatment with adalimumab or placebo and all continued treatment with methotrexate. The IMP was stopped after a maximum of 18 months or after treatment failure within this time, after which they were followed-up for 6 months as per trial protocol. This study includes data from the SYCAMORE trial and retrospective data from ongoing follow-up. For clarity,

reference will be made to ‘trial’ (the SYCAMORE trial) and ‘study’ (this study, following on from the SYCAMORE trial follow-up period). Participants were commenced on adalimumab after the IMP was withdrawn as considered clinically indicated. Figure 1 represents the pathway and time course and treatment course. All patients were included for analysis (including trial treatment failures and trial withdrawals). Continuous data are summarized using means and standard deviation.

Results

Patients

All 28 participants of the SYCAMORE trial recruited at the Bristol Eye Hospital were included in this study (31% of the total SYCAMORE cohort). The first Bristol participant underwent randomization on 27/10/2011 and the final patient on 05/02/2015. The last SYCAMORE trial visit was the 15/09/2016. Nineteen participants were randomized to adalimumab, nine to placebo. The median follow-up period of this study from the date of randomization (and therefore beyond the end date of the trial) was 1483 days (range 195 – 2016 days) and 9 (32%) participants were followed-up for 5 years (1825 days) or more.

The mean age at the final SYCAMORE visit was 10.25 years (SD 4.49) and 20 children were female (72%). Further baseline participant characteristics are summarized in Supplementary Table 1.

Uveitis activity and treatment course

Figure 1 shows participant numbers after randomization and subsequent treatment course. During the follow-up period of this study (after the end of trial and with cessation of IMP), 26 of the 28 patients had a flare of their JIA-U. The median time to flare following the last dose of IMP in the SYCAMORE trial was 150 days 95% CI (44,200) (Figure 2).

Twenty-five patients started adalimumab after their last dose of trial IMP (two started immediately after IMP was withdrawn at the end of the trial and 23 started following a subsequent flare after IMP was withdrawn) (Figure 1, rows 3 and 4). Eleven of these patients subsequently had a flare whilst on adalimumab. The median time to flare following the start of adalimumab (during the extended follow-up period) was 986 days 95% CI (436,1450) (Supplementary Figure 1).

Five patients subsequently stopped adalimumab that had been started after the end of the trial (Figure 1, row 8). Three of these participants stopped adalimumab after a two-year period of disease inactivity during this study following the recommencement of adalimumab after the trial. All three had a flare of uveitis on subsequent methotrexate monotherapy (42-149 days after the final dose of adalimumab).

All participants continued methotrexate until the end of the trial follow-up period and methotrexate was not automatically withdrawn along with the IMP. Five participants stopped methotrexate during the extended study follow-up period (four participants

due to the development of intolerable side-effects and one participant after 3 years of uveitis inactivity at 1343 days post-randomization for the SYCAMORE trial). All participants were treated with topical steroids at the time of flare.

Adalimumab group

Twelve children completed the adalimumab arm of the trial, 11 (92%) of whom had a flare of uveitis during the extended study follow-up period after stopping the IMP. The median time to flare from final IMP in this group of 11 participants was 188 days (range 42 - 413). All 11 were restarted on adalimumab due to active JIA-U (median 217 days and range 50 - 484 from final SYCAMORE trial IMP) and continued until the end of the follow-up period.

Placebo group

Only one of the participants in the placebo arm completed the trial. Time to flare from final IMP treatment was 511 days. Seven (78%) of the 9 participants in the placebo group were subsequently treated with adalimumab following a flare of uveitis. One patient declined adalimumab and was treated with infliximab.

Visual outcomes

Twenty-seven of the total 28 Bristol participants demonstrated no unexplained or sustained reduction in vision from baseline of >0.3 LogMAR units over two consecutive readings over any 3-month period during the extended study follow-up period. Mean visual acuity for these 27 participants in LogMAR units at the end of the extended study follow-up period was -0.04 (right eye), -0.05 (left eye), ranging from -0.25 to 0.20. Only one participant, who had been treated with topical steroids, showed a sustained reduction in vision from -0.10 to 0.30 due to cataract formation.

Complications

Four (14%) participants developed a cataract during the extended study follow-up period. Three maintained visual acuity in the affected eye of at least LogMAR 0.00 and none had surgery. Three (11%) participants developed ocular hypertension of >25mmHg, two of whom were on topical steroids for a JIA-U flare. The intraocular pressure normalized in each participant with the resolution of the flare and/or cessation of topical steroids. The third participant required a Baeveldt tube implant for treatment of glaucoma on day 1624 post-randomization. This participant had failed triple-therapy topical glaucoma medication. Two patients (3 eyes) had posterior synechiae at baseline and at the end of the extended study follow-up period. No other complications were recorded.

Adverse events

The total number of patient years during follow-up was 81.62 and a total of 30 adverse events (AE) were recorded in 10 participants during the available follow-up period after cessation of the IMP (see Supplementary Figure 2). The AE rate per 100 patient days was 0.10 95% CI (0.06 to 0.14). Minor infections were the most commonly recorded events. One participant was admitted to hospital for intravenous antibiotics and drainage of a leg abscess.

Discussion

This retrospective interventional case series of all participants of the SYCAMORE study from a single trial center supports a longer-term role for adalimumab in the treatment of refractory JIA-U. For the majority of children, drug-induced remission of JIA-U did not persist when adalimumab was withdrawn after 1-2 years of treatment on the trial. As such, eleven (92%) of the participants on the active treatment arm who completed the SYCAMORE trial were subsequently restarted on adalimumab because of relapse of uveitis. The median time to flare after stopping the trial adalimumab in this group was 188 days, whereas the time to flare was extended to a median of 986 days in the 25 participants on adalimumab after the IMP had been withdrawn. A small retrospective case series of pediatric uveitis showed that uveitis flared within 3 – 7 months of stopping adalimumab, in keeping with our findings [14]. Extending the duration of adalimumab treatment is costly however and carries the risk of adverse events; one child in this study had a severe infection requiring hospital admission while on adalimumab.

Adalimumab was well tolerated and was only stopped due to ineffectiveness in two children. This is in keeping with emerging longitudinal data on JIA from the German biologics register [15]. JIA-U is associated with a significant risk of sight loss, but in this cohort children maintained excellent visual acuity with just one eye having reduced visual acuity secondary to cataract [4,5]. Limitations of the study include variable follow-up duration and missing data due to the fact that data collection was retrospective. Participants were enrolled from a single centre in the SYCAMORE trial, therefore the sample size is small and selective (n=28). This was a challenging group of children with JIA-U that was refractory to at least 12-weeks methotrexate treatment, and who had treatment with methotrexate plus adalimumab for 1-2 years. The conclusions of this study cannot therefore be applied to mild-moderate forms of JIA-U. Finally, uveitis activity was recorded using SUN anterior chamber cell scores; there was no access to anterior chamber flare photometry which may be helpful in measuring a response to therapy.[16,17]

In summary, this study supports a continued role for adalimumab in JIA-U, but not without safety and cost considerations. The method of withdrawing adalimumab requires further exploration, as participants who stopped adalimumab did so suddenly, and the optimal duration of treatment also remains unclear.

Disclosure statement

Catherine Guly has sat on an advisory board for Abbvie and has received speaker fees from AbbVie, Novartis and Eli Lilly. Andrew Dick consults for AbbVie and Novartis. Athimalapet Ramanan is the co-chief investigator of the SYCAMORE study funded by the NIHR and Arthritis Research UK. He receives speaker fees/honoraria from Abbvie, SOBI, Eli Lilly, UCB and Roche. Ashley Jones and Ben Hardwick were co-authors of the SYCAMORE study and as part of the data sharing agreement between University Hospitals Bristol NHS Foundation Trust and AbbVie; the Clinical Trials Research Centre and the University of Liverpool have produced Clinical Study Reports in support of regulatory submissions by Abbvie.

Funding sources

The research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Acknowledgements

Richard Lee and Andrew Dick are supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

References

1. Saurenmnn RK, Levinn AV, Feldmn BM, et al. Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term follow-up study. *Arthritis Rheum* 2007;56(2):647-57.

2. Kotaniemi K, Kautiainen H, Karma A, Aho K. Occurence of uveitis in recently diagnosed juvenile chronic arthritis: a prospective study. *Ophthalmology* 2001;108(11):2071-5.

3. BenEzra D, Cohen E, Maftzir G. Uveitis in children and adolescents. *Br J Ophthalmol* 2005;89(4):444-48.

4. Ozdal PC1, Vianna RN, Deschênes J. Visual outcome of juvenile rheumatoid arthritis-associated uveitis in adults. *Ocul Immunol Inflamm* 2005;13(1):33-8.

5. De Boer J, Wulffraat N, Rothova A. Visual loss in uveitis of childhood. *Br J Ophthalmol* 2003;87(7):879-84.

6. Heinz C, Mingels A, Goebel C, et al. Chronic uveitis in children with and without juvenile idiopathic arthritis: differences in patient characteristics and clinical course. *A J Rheumatol* 2008;35(7):1403-7.

7. Sen ES, Morgan MJ, MacLeod R, et al. Cross sectional, qualitative thematic analysis of patient perspectives of disease impact in juvenile idiopathic arthritis-associated uveitis. *Ped Rheumatol Online* 2017;15:58. https://doi.org/10.1186/s12969-017-0189-6

8. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2005;32(2):362–5.

9. Cann M, Ramanan AV, Crawford A, et al. Outcomes of non-infectious paediatric uveitis in the era of biologic therapy. *Ped Rheumatol Online* 2018;16(1):51.

10. Simonini G, Paudyal P, Jones GT, Cimaz R, Macfarlane GJ. Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach. *Rheumatology* 2013;52(5):825–31.

11. Ramanan AV, Dick AD, Jones AP et al. Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis. *N Engl J Med* 2017;376:1637-1646.

12. European Medicines Agency. European public assessment report: Humira. Available at: http://www.ema.europa.eu. Accessed June 4, 2019.

13. Trusko B, Thorne J, Jabs D, et al. The Standardization of Uveitis Nomenclature (SUN) Project. Development of a clinical evidence base utilizing informatics tools and techniques. *Methods Inf Med* 2013;52(3):259-65.

14. Castiblanco C, Meese H, Foster C S. Treatment of pediatric uveitis with adalimumab: the MERSI experience. *Journal of AAPOS* 2016;20(2):145-147.

15. Klotsche J, Niewerth M, Haas JP, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). *Ann Rheum Dis* 2016;75(5):855-61.

16. Ramanan AV, Guly C. Adalimumab for childhood onset uveitis. *Ann Rheum Dis* 2018;77(7):961-962.

17. Quartier P, Baptiste A, Despert V, et al. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic juvenile idiopathic arthritis-associated anterior uveitis. *Ann Rheum Dis* 2018;77(7):1003-1011.

Figure captions

Figure 1. Trial grouping and treatment course.

Figure 2. Kaplan Meier plot showing survival to flare in days after cessation of the SYCAMORE investigational medicinal product (IMP). Twenty-six Bristol participants were included; two did not flare after stopping the IMP and were therefore censored