***Author: This file is the accepted version of your manuscript, and it shows any changes made by the Editor-in-Chief and the Deputy Editor since you submitted your last revision. This is the version that is being sent to Manuscript Editing for further editing in accordance with NEJM style. You will receive proofs of the edited manuscript, by e-mail. The proofs will contain queries from the manuscript editor, as well as any queries that may be present in this file. The proof stage will be your next opportunity to make changes; in the meantime, please do not make any changes or send any new material to us.***

**Adalimumab in Combination with Methotrexate for JIA-Associated Uveitis**

Athimalaipet V. Ramanan, F.R.C.P.C.H., F.R.C.P..1, Andrew D. Dick, M.B., B.S., M.D.2,3, Ashley P. Jones4, Andrew McKay4, Paula R. Williamson, Ph.D.4, Sandrine Compeyrot Lacassagne, M.D.5, Ben Hardwick, B.Sc., M.Res.4, Helen Hickey4, Dyfrig Hughes, Ph.D.6, Patricia Woo, F.Med.Sci.3, Diana Benton1, Clive Edelsten, M.R.C.P., F.R.C.Ophth.5, Michael W. Beresford, M.B., Ch.B., Ph.D.,4,7 on behalf of the SYCAMORE Study Group\*.

1 University Hospitals Bristol NHS Foundation Trust, Bristol, UK, 2 Bristol Eye Hospital, Bristol, UK, 3 School of Clinical Sciences, University of Bristol, UCL Institute of Ophthalmology and National Institute for Health Research (NIHR) Biomedical Research Centre at Moorfields Eye Hospital and University College London Institute of Ophthalmology, 4Institute of Translational Medicine, University of Liverpool, Liverpool, UK, 5 Great Ormond Street Hospital, Great Ormond Street, London, WC1N 3JH UK, 6 Bangor University, College Road, Bangor, LL57 2DG UK, 7 Department of Paediatric Rheumatology, Alder Hey Children’s NHS Foundation Trust, Liverpool, UK

\* A complete list of the investigators in SYCAMORE Study Group is provided in the Supplementary Appendix, Table S1, available at NEJM.org

**Address for correspondence:**

Prof. A. V. Ramanan

Department of Paediatric Rheumatology

Bristol Royal Hospital for Children

Bristol, UK, BS28BJ

Email – avramanan@hotmail.com

Word Count (not including Abstract): 2525

**ABSTRACT**

**Background:** Adalimumab, a fully human anti–TNF monoclonal antibody, is effective in juvenile idiopathic arthritis (JIA). We have tested the efficacy of adalimumab in the treatment of JIA- associated uveitis.

**Methods:** A multicenter double-blind, randomised placebo-controlled trial assessed the efficacy and safety of adalimumab in children aged 2 to 18 years with active JIA-associated uveitis. Patients on a stable dose of methotrexate were randomly assigned to adalimumab (20mg or 40mg subcutaneously based on body weight) or placebo, fortnightly, in a 2:1 ratio. Patients were treated until treatment failure or until 18 months had elapsed. They were followed for two years after randomisation. The primary endpoint was time to treatment failure defined by a multi-component, intraocular inflammatory score, based on Standardised Uveitis Nomenclature criteria.

**Results:** Ninety patients were enrolled when the pre-specified stopping criteria were met; we enrolled no further patients (we had planned to enrol 114). We observed 16 (27%) treatment failures in 60 patients receiving adalimumab versus 18 (60%) treatment failures in 30 receiving placebo (HR 0.25 (95% CI: 0.12,0.49); p<0.0001). Adverse events (10.07; 95% CI: 9.26,10.89 versus 6.51; 95% CI: 5.26,7.77 per patient year) and serious adverse events (0.29; 95% CI: 0.15,0.43 versus 0.19; 95% CI: 0,0.40 per person year) were reported more frequently in patients receiving adalimumab versus those receiving placebo.

**Conclusions:** Adalimumab controlled inflammation and reduced the rate of treatment failure in patients with active uveitis on a stable dose of methotrexate. Adalimumab-treated patients had a much higher incidence of adverse and serious adverse events. (EudraCT 2010-021141-41)

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease. Children with JIA are at risk of inflammation of the uvea (uveitis). Approximately 12-38% of patients with JIA develop uveitis within seven years of onset of arthritis (1, 2). Despite current screening and therapeutic options, up to 15% of children with JIA-associated uveitis may develop bilateral visual impairment and be certified legally blind (3, 4).

Experimental models of autoimmune uveitis demonstrate that tumor necrosis factor alpha (TNF-α) plays a pivotal role in pathogenesis (5), borne out in treatment of adult uveitis (6-8) and pediatric case series (9-14) (15-17). Adalimumab is a fully human anti–TNFα monoclonal antibody. A multicenter randomized, double-blind, parallel group trial has shown significant benefit in children with active rheumatoid arthritis (18). We carried out the SYCAMORE Trial to assess the role of adalimumab in the treatment of methotrexate (MTX)-refractory JIA-associated uveitis.

**METHODS**

We conducted a multicenter, double-blind, randomised placebo-controlled trial. The primary outcome was the efficacy of adalimumab in children with active JIA-associated uveitis, as measured by scores noted below, despite stable MTX treatment for at least 12 weeks.

**Protocol and Study Population**

An independent ethics committee and the Medicines for Healthcare Regulatory Agency approved the trial protocol. Each parent/guardian provided written informed consent and each child gave their assent where appropriate. The trial protocol (19)is available at NEJM.org, and the authors vouch for the fidelity of this report and the trial to the protocol. AbbVie had no part in study design, collection or analysis of the data, or manuscript preparation. AbbVie Inc. reviewed the final draft of the manuscript. All of the authors assume responsibility for the accuracy and completeness of the data.

Patients aged 2 to <18 years with active JIA-associated uveitis, despite a stable weekly dose of MTX treatment for at least 12 weeks, were eligible for randomisation. Stable MTX treatment required dose (10-20mg/m2, maximum dose of 25mg/patient) and route to remain constant. Active uveitis was defined as ‘sustained grade of cellular infiltrate in anterior chamber of Standardization of Uveitis Nomenclature (SUN) (20) criteria grade >1+ during the 12 weeks prior to screening despite MTX and corticosteroid (systemic and/or topical) therapy’ on at least two occasions. Key exclusion criteria included: prior exposure to adalimumab; prior exposure to another biologic agent such that the estimated level of drug in patient’s blood is less than that predicted by 5-half-lives of the drug; on more than six topical steroid eye drops per eye per day; on prednisone (or equivalent) at a dose exceeding 0.2mg/kg per day. Full inclusion/exclusion criteria, and concomitant medications permitted and not permitted, are described in the study protocol (which can be found at NEJM.org) (19).

**Randomization and Study Procedures**

Randomization was performed using a web-based system with random permuted block sizes of 3 and 6, stratified by center. At enrolment, eligible patients were allocated in a 2:1 ratio to either receive adalimumab or placebo respectively.

Study visits were scheduled at 4, 8, and 12 weeks, and then every 12 weeks until 18 months, or until a participant stopped study treatment, at which point they were followed for another six months.

Ophthalmic assessment of disease activity and ocular complications were measured throughout the study using slit lamp bio-microscopy for uveitis activity, using the SUN criteria (20) (Table S2 in Supplementary Appendix). The primary and secondary outcomes were assessed at each study visit and at any unscheduled visits.

**Trial Treatment**

We recruited patients between 1 October 2011 and 10 April 2015. The first patient was randomized on the 27th October 2011 and the final patient was randomized on the 31st March 2015.

All participants received a stable dose of weekly oral or subcutaneous MTX (10-20mg/m2 per dose, maximum 25mg/patient). No dose reduction or change in route of administration was allowed. Dose increase was acceptable for somatic growth (so that the dose/m2 at trial entry was maintained throughout the trial) but not on clinical grounds. Participants received either adalimumab (20mg/0.8ml for patients <30kg; 40mg/0.8ml for patients ≥30kg), or placebo (0.8ml) subcutaneous injection, fortnightly. AbbVie Inc. provided the investigational medicinal product (adalimumab) and matching placebo in identical pre-filled vials.

**Trial Outcomes**

**Primary End Point**

The primary end point was ‘time to treatment failure’, defined by at least one of the following criteria being met: i) 2 grade increase from baseline in SUN cell activity score (Anterior Chamber Cells) over 2 consecutive visits (the score is proportional to the approximate number of cells per one square millimetre;20 the higher the score, the greater the number of cells. There are no internationally agreed-upon minimally important differences in this scale); ii) sustained non-improvement of SUN cell activity score with entry grade of >3 for two consecutive readings (apart from baseline); iii) only partial improvement (1 grade) or no improvement, from baseline, with development of other ocular co-morbidity which is sustained over two consecutive visits; iv) worsening of existing (on enrolment) ocular co-morbidity after three months; v) entry grade (grades 1 or 2 in SUN cell activity score) still present after 6 months of therapy and has been sustained over two consecutive visits; vi) use of ineligible concomitant medications (not in pre-defined acceptable criteria or those not allowed); vii) intermittent or continuous suspension of study treatment for a cumulative period longer than four weeks. All study assessments were carried out by persons without knowledge of treatment allocation.

**Secondary Outcomes**

All secondary outcomes were assessed at each study visit (19) (and listed in Table S8, Supplementary Appendix). These included: use of topical and systemic glucocorticoids; flare of uveitis defined by SUN criteria; control, remission, and duration of inactive disease (uveitis); health-related quality of life (CHAQ (21): scale 0-3, minimal clinically important difference (MCID): -0.188 for improvement and +0.125 for worsening; and CHQ (22): scale 0-100, higher scores indicate better or more positive health states, no specific MCID recognised); flare of JIA, remission on and off medication (23), minimum JIA disease activity (24) (oligoarticular JIA: physician’s global assessment (PhGA) <2.5cm and no swollen

Joints; polyarticular JIA: PhGA <3.4 cm, patient/parent global assessment (PaGA) <2.1 cm, and <1 swollen joint), Juvenile Arthritis Disease Activity Score (JADAS) (25) (Linear sum of four components: (i) PhGA: 010cm VAS, (ii) PhGE: 010cm VAS, (iii) Active joint count assessed in one of three ways: JADAS-10: any involved joint up to a maximum of 10 JADAS-27: 27 joints including cervical spine, elbows, wrists, first to third metacarpophalangeals, proximal interphalangeals, hips, knees and ankles, JADAS-71: all 71 joints (iv) ESR: Normalized on a 0-10 scale using the formula below to avoid excessive weight in the overall index: [ESR (mm/h)20]/10; minimum disease activity 2 for oligoarticular and 3.8 for polyarticular disease) and the Standard American College of Rheumatology (ACR) pediatric core outcome set variables (26).

See supplementary Table S8 for a description of post-hoc analyses.

**Safety**

All participants receiving at least one dose of adalimumab or placebo were included in the safety analyses. Adverse events (AEs) were recorded and reported from first study drug dose at each visit, regardless of severity or perceived association with trial intervention. Serious AEs (SAEs) were collected from the time of informed consent. AEs were tabulated using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 system organ class and preferred terms.

**Statistical Analysis**

The trial was originally designed with 90% power to detect a 50% relative reduction from 60% to 30% in the rate of treatment failure at a 5% significance level (two-sided). In view of significant early recruitment challenges, the independent data and safety monitoring committee and trial steering committee, approved by the trial funders, advised protocol amendment, reducing the power to 80%, requiring 114 patients recruited (76 adalimumab and 38 placebo), including a 5% inflation for missing primary outcome data.

Intention-to-treat analysis of the primary outcome was undertaken. The log-rank test was performed to investigate between-group comparisons, and Kaplan-Meier plots presented to illustrate the distribution of time to treatment failure. The hazard ratio (HR) and 95% confidence interval (95%CI) were estimated after fitting a Cox proportional hazards model with the assumption of proportional hazards checked via the addition of a time-dependent treatment effect parameter to the model. A two sided p-value of <0.001 was used for the Haybittle-Peto stopping boundary for the interim analysis and a two sided p-value of <0.05 considered statistically significant for the final analysis (27). Pre-specified sensitivity analyses tested impact of missing data, participants who stopped their intervention early and those who had been incorrectly identified as having failed treatment. The statistical analysis plan includes full details of sensitivity analyses. Analyses were performed using SAS® version 9.3 (SAS Inc., USA).

**Trial Oversight and Trial Stopping**

After the second interim analysis, the data safety monitoring committee noted on 11th March 2015 that there were 27 treatment failures reported among 90 randomized participants through to the 20th January 2015. The adalimumab group showed evidence of a highly significant reduction in the risk of treatment failure (log rank p-value p<0.0001; HR 0.25 95%CI 0.11,0.53). On the basis of formal stopping boundaries (27), the data safety monitoring committee recommended recruitment to the trial should cease, all participants should be subsequently un-blinded, placebo-treated participants should cease treatment and enter trial follow-up, and participants receiving adalimumab should continue as per study protocol. Following consultation between the data safety monitoring committee, the trial steering committee, and then with the Co-Chief Investigators (AVR, MWB), a decision was made to implement this recommendation, with support of the study team (who had remained blinded throughout) and agreement of the study sponsor and funders. Patients were called in for final blinded treatment response assessments. Patients on adalimumab were asked to continue as per protocol for the duration of the study in an open label follow up until completion of their 18-month treatment, an adverse event attributed to drug that precluded continued treatment, or until treatment failure. All patients who received placebo stopped trial treatment and completed the six month follow-up phase of the study. Open-label extension of the trial continues.

**RESULTS**

**Study Participants**

Of 332 participants screened, attending 14 UK sites, 242 were not randomised because they did not meet inclusion/exclusion criteria. Sixty participants (Table 1) were randomised to adalimumab and 30 to placebo (Figure S1, Supplementary Data). Primary outcome data were available for all randomised participants.

Nine (15%) adalimumab-treated patients and seven (23%) placebo-treated patients discontinued the trial intervention for reasons other than treatment failure (see Figure S1). Seven of these adalimumab-treated participants and six of these placebo-treated participants agreed to be subsequently followed.

**Treatment Failure**

The addition of adalimumab to MTX significantly delayed the time to treatment failure compared to placebo (logrank p-value p<0.0001; HR 0.25, 95%CI 0.12,0.49)(Figure 1A). Median time to treatment failure was 24.10 weeks (95%CI 12.40,26.00) in the placebo group and not reached in the adalimumab group within the 18-month treatment period (Figure 1A). A significantly higher proportion of patients treated with placebo 18/30 (60%) failed treatment compared to those treated with adalimumab (16/60, 27%; p=0.002; relative risk 0.40 (0.22, 0.73))(Table S3 and S4). Nine sensitivity analyses confirmed the conclusion found in the primary analysis (Table S5).

**Safety and Adverse Events**

Summary data of AEs are listed in Table 2, and SAEs in Table 3. A total of 588 AEs were reported in 53 (88%) patients in the adalimumab group and 103 AEs reported in 25 (83%) patients in the placebo group. The rate of SAEs was 0.29 (95% CI: 0.15,0.43) versus 0.19 (95% CI: 0.00,0.40) per-person-year, and the rate of AEs was 10.07 (95% CI: 9.26,10.89) versus 6.51 (95% CI: 5.26,7.77) per-person-year, were both greater in the adalimumab-treated group. For full listing of all adverse events see Table S6 and S7.

**Secondary Outcomes**

A full summary of secondary outcome analyses is available in Table S8, Supplementary Appendix.

At randomisation, six participants (5 adalimumab, 1 placebo) were on systemic glucocorticoids (permitted dose: <0.20mg/kg/day; median dose for both groups, 0.14mg/kg). Three adalimumab-treated participants stopped systemic glucocorticoids (median duration 18.1 weeks). The placebo patient stopped systemic glucocorticoids after 5.6 weeks.

Of 63 participants on ≥2 drops of topical glucocorticoids at randomisation, a significantly greater proportion of adalimumab-treated patients had a reduction to <2 drops (n=22/45 (49%)) compared to placebo-treated patients (n=3/18 (17%), (HR=3.47 95%CI (1.01, 11.95), p=0.049), see Figure 1B. Of 74 participants on ≥1 drop at randomisation, there was a significantly greater proportion of adalimumab-treated patients who had a reduction in their topical corticosteroid dose to 0 drops (n=23/49 (47%)) compared to placebo-treated patients (n=4/25 (16%), (HR=3.38 95%CI (1.24, 10.32), p=0.02) (see Figure S2).

Adalimumab-treated patients had a significantly longer mean duration of sustained inactive disease (zero cells) compared to those receiving placebo (179.28 days (SE:16.91) versus 14.50 days (SE:23.94); estimated treatment effect 164.79 95%CI (104.41, 225.16), p<0.0001). Those on adalimumab were on treatment for twice as long (345.03 days (SD:165.41) versus 159.27 (SD:154.22)).

Arthritis flare occurred in three patients (10%) in the placebo-treated arm during the treatment period, compared to none in the adalimumab treated group [RR=0.07, 95% CI (0.004, 1.36), p=0.03]. As most of the children entered the study with minimal arthritis (Table 1) the ACR 30, 50, 70, 90 and 100 (see Table S11, Supplementary Appendix) and JADAS 10, 27 and 71 (see Table S12, Supplementary Appendix) were only minimally impacted. There was no significant difference in health-related quality of life (CHQ and CHAQ) across time between treatment groups (see Table S13 and Table S14).

**Post hoc analyses**

Time-to-treatment response (see Figure S3) demonstrates a difference between the two groups in favour of adalimumab (log rank exploratory p-value=0.003; HR 3.15 95%CI 1.42, 7.00). There was a difference in the proportion of responders at three and six months in favour of adalimumab (exploratory p-values=0.004 and p=0.004 respectively). Thirty-four (57%) adalimumab-treated and five (17%) placebo-treated participants were classified as having responded to treatment (Table S15).

**DISCUSSION**

In this randomised, placebo-controlled trial in JIA-associated uveitis, treatment with adalimumab significantly delayed time to treatment failure compared with MTX alone (p<0.0001; HR 0.25 (95% CI 0.12,0.49)). A significantly greater proportion of adalimumab-treated patients, when compared with placebo-treated patients, had a reduction in their topical corticosteroid dose (HR 3.47 (1.01, 11.95), p=0.049). A significantly greater number of adalimumab-treated patients discontinued topical glucocorticoids (HR 3.38 (1.24, 10.32), p=0.02).

However, there were many more adverse events and more severe adverse events in the adalimumab group than in the placebo group. The most common adverse events in the adalimumab group were minor infections, respiratory disorders and gastrointestinal disorders. The rate of adverse events per patient year was higher in the adalimumab-treated group (10.07 vs 6.57). The number of SAEs was also higher in the adalimumab-treated group. The follow-up period during the course of the study was not long enough to detect events such as malignancies and de-myelinating diseases. Sample size precludes commentary regarding rarer events.

Limitations of the study include the use of anterior chamber cell count (SUN criteria) as a component of the primary outcome. Although internationally recognised, the SUN criteria have not been validated for use in children. All participating clinicians were instructed in the assessment of SUN criteria.

In conclusion, adalimumab in combination with MTX is an effective therapy for children with JIA-associated uveitis although the drug is associated with a higher incidence of adverse and serious adverse events.

**Disclosure:**

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

**Acknowledgements:**

This project was funded by the National Institute for Health Research Health Technology Assessment Programme (project 09/51/01) and Arthritis Research UK (grant reference 19612).

The authors would like to acknowledge and thank the significant support by the National Institute of Health Research (NIHR) Clinical Research Network (CRN) Children (https://www.crn.nihr.ac.uk/children/) in supporting the set up and delivery of this trial.

The SYCAMORE TMG would like to thank the help and support of the two independent committees that had independent oversight of the trial, these were the Trial Steering Committee (TSC) (Chair: Professor Ian Bruce, Dr. Carlos Pavesio and Mr. Matthew Sydes) and the Independent Data and Safety Monitoring Committee (Chair: Professor John Sparrow, Professor Steff Lewis, Professor Justine Smith and Dr. Nico Wulffraat). Thanks are also due to Dr. Janine Grey who was an independent member of the TSC before having to leave her role.

The SYCAMORE TMG would like to acknowledge and thank all participating centres, the multi-disciplinary teams supporting the trial, and all children, young people and families who took part in this trial.

University Hospitals Bristol NHS Foundation Trust, as Sponsor of Study has a data sharing agreement with AbbVie in support of regulatory purposes.

The authors would like to acknowledge and thank AbbVie Inc. for providing active drug and placebo used in the trial.

**References**

1. Kotaniemi K, Kautiainen H, Karma A, Aho K. Occurrence of uveitis in recently diagnosed juvenile chronic arthritis: a prospective study. Ophthalmology.108:2071-5.

2. Saurenmann R, Levin A, Feldman B, Rose J, Laxer R, Schneider R, et al. Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term followup study. . Arthritis Rheum 2007;56:647-57.

3. Wolf M, Lichter P, Ragsdale C. Prognostic factors in the uveitis of juvenile rheumatoid arthritis. Ophthalmology. 1987;94:1242-8.

4. de Boer J, Wulffraat N, Rothova A. Visual loss in uveitis of childhood. Br J Ophthalmol. 2003;87:879-84.

5. Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU). Prog Retin Eye Res 2004;23:617-37.

6. Imrie FR, Dick AD. Biologics in the treatment of uveitis. Curr Opin Ophthalmol 2007;18(481-486).

7. Levy-Clarke G, Jabs D, Read R, Rosenbaum J, Vitale A, Van Gelder R. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patinets with ocular inflammatory disorders. Opthalmology. 2014;1221(3):785-96.

8. Cordero-Coma M, Yilmaz T, Onal S. Systematic review of anti-tumor necrosis factor-alpha therpay for treatment of immune-mediated uveitis. Ocul Immunol Inflamm. 2013;21(1):19-27.

9. Biester S, Deuter C, Michels H, Haefner R, Kuemmerle-Deschner J, Doycheva D, et al. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol 2007;91:319-24.

10. Foeldvari I, Nielsen S, Kummerle-Deschner J, Espada G, Horneff G, Bica B, et al. Tumor necrosis factor-alpha blocker in treatment of juvenile idiopathic arthritis-associated uveitis refractory to second-line agents: results of a multinational survey. . J Rheumatol 2007;34:1146-50.

11. Gallagher M, Quinones K, Cervantes-Castaneda R, Yilmaz T, Foster C. Biological response modifier therapy for refractory childhood uveitis. Br J Ophthalmol 2007;91:1341-4.

12. Saurenmann R, Levin A, Rose J, Parker S, Rabinovitch T, Tyrrell P, et al. Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. Rheumatology. 2006;45:982-9.

13. Sharma S, Ramanan A, Riley P, Dick A. Use of infliximab in juvenile onset rheumatological disease-associated refractory uveitis: efficacy in joint and ocular disease. Ann Rheum Dis 2007;66:840-1.

14. Tynjala P, Kotaniemi K, Lindahl P, Latva K, Aalto K, Honkanen V, et al. Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. Rheumatology 2008;47:339-44.

15. Simonini G, Druce K, Cimaz RM, GJ, Jones G. Current evidence of anti-tumour necrosis factor α treatment efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach of individual drugs. Arthritis Care Res. 2014;66:1073-84.

16. Sen E, Sharma S, Hinchcliffe A, Ramanan AV. Use of adalimumab in refractory non-infectious childhood chronic uveitis: efficacy in ocular disease - a case cohort interventional study. Rheumatology. 2012;51(12):2199-203.

17. Sen E, Dick AD, Ramanan AV. Uveitis associated with juvenile idiopathic arthritis. Nat Rev Rheumatol. 2015;11(6):339-48.

18. Lovell D, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med 2008;359:810-20.

19. Ramanan A, Dick A, Benton D, Compeyrot-Lacassagne S, Dawoud D, Hardwick B, et al. A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial). Trials. 2014;15(14).

20. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-16.

21. Nugent J, Ruperto N, Grainger J, Machado C, Sawhney S, Baildam E, et al. The British version of the childhood health questionnaire (CHAQ) and the child health questionnaire (CHQ). Clin Exp Rheumatol. 2001;19 (Suppl 23):S163-S7.

22. Oliveira S, Ravelli A, Pistorio A, Castell E, Malattia C, Prieur AM, et al. Proxy-reported health related quality of life of patients with juvenile idiopathic arthritis: the Paediatric Rheumatology International Trials Organisation multinational quality of life cohort study. Arthritis Rheum. 2007;1:35-43.

23. Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. 2004. 2004;31:2290-94.

24. Magni-Manzoni S, Ruperto N, Pistorio A, Sala E, Solari N, Palmisani E, et al. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. Arthritis Rheum. 2008;59:1120-27.

25. Consolaro A, Rupero N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum. 2009;61(5):658-66.

26. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum. 1997;40:1202-09.

27. Pocock SJ. Current controversies in data monitoring for clinical trials. Clinical Trials. 2006;3(6):513-21.

Figure Legend

Figure 1: Treatment Failure and topical corticosteroid dose over time

A: Kaplan Meier Plot – Time to Treatment Failure

**B:** Cumulative incidence plot – Reduction in topical glucocorticoid dose

**Table 1: Baseline characteristics of the participants**

|  |  |  |
| --- | --- | --- |
| Characteristic | Adalimumab (N=60) | Placebo (N=30) |
| Eligible Eyes – Unilateral - N(%) | 43 (72) | 22 (73) |
| Weight <30kg – N(%) | 33 (56) | 17 (57) |
| Age (years)\* | 9.07 ± 3.94 | 8.56 ± 3.79 |
| Female sex – N(%) | 47 (78) | 23 (77) |
|  |  |  |
| Ophthalmology Characteristics | **Adalimumab (N α =77)** | **Placebo (N α =38)** |
| LogMAR Score\* | 0.04 ± 0.15 | 0.07 ± 0.12 |
| AC cells (SUN) – N(%) |  |  |
| 1+ | 52 (68) | 24 (63) |
| 2+ | 18 (23) | 11 (29) |
| 3+ | 6 (8) | 3 (8) |
| 4+ | 1 (1) | 0 (0) |
| Flare Score (SUN) – N(%) |  |  |
| 0 | 18 (23) | 12 (32) |
| 1+ | 49 (64) | 23 (61) |
| 2+ | 10 (13) | 3 (8) |
| Intraocular pressure mmHg\* | 14.76 ± 3.85 | 14.11 ± 4.27 |
| Vitreous Haze Grading – N(%) |  |  |
| 0 | 65 (84) | 32 (84) |
| 0.5+ | 8 (10) | 4 (11) |
| 1+ | 3 (4) | 2 (5) |
| 2+ | 1 (1) | 0 (0) |
| Topical steroid drops\* | 2.31 ± 1.44 | 2.25 ± 1.54 |
|  |  |  |
| Opthalmic Complications |  |  |
| Central band-keratopathy – N(%) | 2 (3) | 0 (0) |
| Synchiae – N(%) | 18 (23) | 6 (16) |
| Iris bombe – N(%) | 0 (0) | 0 (0) |
| Membrane formation – N(%) | 2 (3) | 0 (0) |
| Neovascularisation – N(%) | 0 (0) | 0 (0) |
|  |  |  |
| Rheumatology Characteristics | **Adalimumab (N=60)** | **Placebo (N=30)** |
| Type of JIA (ILAR classification) – N (%) |  |  |
| Extended oligoarthritis | 14 (23) | 7 (23) |
| Persistent oligoarthritis | 36 (60) | 17 (57) |
| Polyarthritis RF negative | 8 (13) | 4 (13) |
| Polyarthritis RF positive | 1 (2) | 1 (3) |
| Psoriatic arthritis | 1 (2) | 1 (3) |
| JIA Disease duration (years) | 5.58 ± 3.69 | 4.81 ± 3.19 |
| Physical global assessment of disease activity\* | 0.76 ± 1.48 | 0.83 ± 1.09 |
| Rheumatoid factor – N(%)\*\* | 1 (2) | 3 (10) |
| Anti-nuclear antibody – N(%)\*\* | 33 (55) | 15 (50) |
| Active joint count\*\*\* | 0.00 [0.00, 0.00] | 0.00 [0.00, 2.00] |
| Swollen joint count\*\*\* | 0.00 [0.00, 0.00] | 0.00 [0.00, 2.00] |

N = Number; \*= Mean +/- SD; α = Refers to the total number of eyes; \*\* RhF not available in 13 and 7 patients, and ANA in 3 and 5 patients respectively, on clinical grounds; \*\*\*= Median [Lower quartile, Upper quartile]

Table 2: Number and percentage of patients with adverse events in the adalimumab Group, for events experienced by >= 5% patients (placebo included for comparison)

|  | **Adalimumab**  **N=60** | **Placebo**  **N=30** |
| --- | --- | --- |
|  |  |  |
| **Blood and lymphatic system disorders** |  |  |
| Lymphadenopathy | 3 (5%) | 0 (0%) |
| **Eye disorders** |  |  |
| Eye pain | 4 (7%) | 0 (0%) |
| **Gastrointestinal disorders** |  |  |
| Abdominal pain | 3 (5%) | 0 (0%) |
| Diarrhoea | 8 (13%) | 1 (3%) |
| Nausea | 5 (8%) | 2 (7%) |
| Vomiting | 18 (30%) | 5 (17%) |
| **General disorders and administration site conditions** |  |  |
| Injection site erythema | 3 (5%) | 1 (3%) |
| Injection site mass | 3 (5%) | 0 (0%) |
| Injection site pain | 5 (8%) | 2 (7%) |
| Injection site pruritus | 3 (5%) | 0 (0%) |
| Injection site reaction | 7 (12%) | 0 (0%) |
| Injection site swelling | 4 (7%) | 1 (3%) |
| Pyrexia | 12 (20%) | 2 (7%) |
| **Infections and infestations** |  |  |
| Ear infection | 6 (10%) | 2 (7%) |
| Impetigo | 3 (5%) | 1 (3%) |
| Lower respiratory tract infection | 8 (13%) | 2 (7%) |
| Nasopharyngitis | 15 (25%) | 7 (23%) |
| Oral herpes | 3 (5%) | 1 (3%) |
| Paronychia | 3 (5%) | 1 (3%) |
| Pharyngitis | 4 (7%) | 0 (0%) |
| Tonsillitis | 12 (20%) | 0 (0%) |
| Upper respiratory tract infection | 4 (7%) | 1 (3%) |
| Urinary tract infection | 9 (15%) | 3 (10%) |
| Varicella | 3 (5%) | 0 (0%) |
| Viral infection | 13 (22%) | 1 (3%) |
| **Injury, poisoning and procedural complications** |  |  |
| Fall | 3 (5%) | 0 (0%) |
| **Investigations** |  |  |
| Alanine aminotransferase increased | 4 (7%) | 1 (3%) |
| Aspartate aminotransferase increased | 3 (5%) | 1 (3%) |
| Intraocular pressure increased | 4 (7%) | 0 (0%) |
| **Musculoskeletal and connective tissue disorders** |  |  |
| Arthralgia | 12 (20%) | 2 (7%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** |  |  |
| Skin papilloma | 5 (8%) | 0 (0%) |
| **Nervous system disorders** |  |  |
| Headache | 12 (20%) | 4 (13%) |
| **Respiratory, thoracic and mediastinal disorders** |  |  |
| Cough | 22 (37%) | 3 (10%) |
| Epistaxis | 3 (5%) | 0 (0%) |
| Oropharyngeal pain | 16 (27%) | 2 (7%) |
| **Skin and subcutaneous tissue disorders** |  |  |
| Rash | 3 (5%) | 1 (3%) |

Table 3: Serious adverse events by treatment group

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Adalimumab**  **Events [Patients] (%)\*** | **Placebo**  **Events [Patients] (%)\*** | **Total Events [Total Patients] (%)\*** |
|  |  |  |  |
| Eye disorders \*\* | 1[1] (2%) | 3[2] (7%) | 4[3] (3%) |
|  |  |  |  |
| Gastrointestinal disorders | 2[2] (3%) | 0[0] (0%) | 2[2] (2%) |
|  |  |  |  |
| Infections and infestations | 10[8] (13%) | 0[0] (0%) | 10[8] (9%) |
|  |  |  |  |
| Nervous system disorders | 1[1] (2%) | 0[0] (0%) | 1[1] (1%) |
|  |  |  |  |
| Respiratory, thoracic and mediastinal disorders | 1[1] (2%) | 0[0] (0%) | 1[1] (1%) |
|  |  |  |  |
| Surgical and medical procedures | 2[2] (3%) | 0[0] (0%) | 2[2] (2%) |
|  |  |  |  |
| Total | 17[13] (22%) | 3[2] (7%) | 20[15] (17%) |
|  |  |  |  |

\* Percentage calculated by dividing by the total number of patients within group

\*\* One adalimumab event and two of the placebo events were ‘uveitis flare requiring hospitalizations and treatment’. One placebo event was ‘worsening of vision with flare of uveitis and macular edema’.