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ORIGINAL ARTICLE

Prevention of Flare Recurrences in Childhood-Refractory Chronic Uveitis: An Open-Label Comparative Study of Adalimumab Versus Infliximab

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Objective. **To compare the efficacy and safety of adalimumab versus infliximab in an open-label prospective, comparative, multicenter cohort study of childhood noninfectious chronic uveitis.**

Methods. **Thirty-three patients (22 females, 11 males, median age 9.17 years) with refractory, vision-threatening, noninfectious active uveitis were enrolled, and received for at least 1 year infliximab (5 mg/kg at weeks 0, 2, and 6, and then every 6–8 weeks) or adalimumab (24 mg/m^2 every 2 weeks). The primary outcome was to assess, once remission was achieved, the time of a first relapse. Time to remission, time to steroid discontinuation, and the number of relapses were also considered.**

Results. **Sixteen children (12 with juvenile idiopathic arthritis [JIA], 3 with idiopathic uveitis, and 1 with Behçet's disease) were recruited in the adalimumab cohort and 17 children (10 with JIA, 5 with idiopathic uveitis, 1 with early-onset sarcoidosis, and 1 with Behçet's disease) were recruited in the infliximab group. Cox regression analysis did not show statistically significant differences between the two groups with regard to time to achieve remission and time to steroid discontinuation, whereas a higher probability of uveitis remission on adalimumab during the time of treatment was shown (Mantel-Cox $\chi^2 = 6.83$, $P < 0.001$). At 40 months of followup, 9 (60%) of 15 children receiving adalimumab compared to 3 (18.8%) of 16 children receiving infliximab were still in remission on therapy ($P < 0.02$).**

Conclusion. **Even if limited to a relatively small group, our study suggests that over 3 years of treatment, adalimumab is more efficacious than infliximab in maintaining remission of chronic childhood uveitis.**

INTRODUCTION

Noninfectious uveitis in childhood is a relatively uncommon severe disease, with potential significant long-term complications such as cataracts, glaucoma, and eventually blindness (1). For these reasons, refractory uveitis usually requires early and aggressive treatment. Immunomodulatory therapy is often needed in order to preserve visual acuity and to prevent significant morbidity of chronic steroid administration (2). Recently, tumor necrosis factor α (TNFα)–blocking agents have been used to treat chronic, refractory uveitis in adulthood as well as in childhood (3). Infliximab, a chimeric human–mouse monoclonal antibody against TNFα, intravenously administered, and adalimumab, a fully human monoclonal antibody against TNFα, subcutaneously injected, have increased the treatment options, albeit in small series and with short followup (4–11). We have recently shown that infliximab appears to be an effective treatment for uveitis in children, but in our experience, its efficacy seemed to wane over time after 1 year of treatment (12).

However, the lack of evidence from head-to-head randomized controlled trials (RCTs) limits our understanding of the best treatment choices, as well as the time of instituting therapy and its duration (4). Up to now, no data

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from comparative studies were available about the efficacy and safety of these 2 anti-TNFα agents.

We recently published in abstract form our single-center, comparative cohort study, suggesting that adalimumab is as efficacious as infliximab in the treatment of sight-threatening childhood uveitis; however, such a pilot study was conducted in a too-small cohort and in a short-term analysis (13).

The purpose of this study was to compare the efficacy and safety of adalimumab versus infliximab in an open-label prospective, comparative, multicenter cohort study of childhood noninfectious chronic uveitis.

MATERIALS AND METHODS

Study design. We conducted an open-label prospective, comparative case series study of pediatric patients with refractory uveitis treated with adalimumab and infliximab for at least a 1-year period at 3 tertiary pediatric rheumatology centers in Italy: Anna Meyer Children's Hospital, Florence; Institute of Child Health IRCCS Burlo Garofolo, Trieste; and Pediatric Clinic, University of Brescia, Brescia.

Inclusion criteria. To be considered eligible for this study, patients were required to have disease onset prior to age 16 years, vision-threatening noninfectious uveitis that was refractory to therapy with systemic corticosteroids and at least 1 other immunosuppressive medication, or to be intolerant to such therapy. "Refractory" was considered persistently active uveitis for at least 3 months despite systemic steroids and immunosuppressive treatment (methotrexate [MTX] and/or cyclosporin A [CSA]).

Study and treatment protocol. At the time of enrollment, medical history and complete rheumatologic and ophthalmologic examinations were performed in addition to a tuberculin purified protein derivative skin test and a chest radiograph. After stopping the previous immunosuppressive therapy (except corticosteroids), eligible children were consecutively enrolled and received 1 of 2 anti-TNFα treatments. Steroid therapy was maintained at a stable dosage (prednisone 1–2 mg/kg/day) for at least 6 weeks, and then tapered once remission was achieved with regard to uveitis activity.

Infliximab infusions were administered at the dose of 5 mg/kg at weeks 0, 2, and 6, and then every 6–8 weeks for at least 1 year. MTX treatment at very low dosages (5–7.5 mg/week) was maintained and/or added to prevent the formation of antiinfliximab autoantibodies. In order to reduce the number of possible covariables influencing our outcome measures, an increased dose of infliximab was not permitted during the time of the protocol, whereas a decreased interval of administration every 6 weeks, a controlled covariable in our analysis, was allowed; therefore, for patients with breakthrough inflammation initially treated with infusions every 8 weeks, a rate escalation to every 6 weeks instead of to a dose escalation was allowed.

The adalimumab group received the drug at 24 mg/m^2 subcutaneously every 2 weeks for at least 1 year. In both groups, therapy was withdrawn if major side effects/complications due to the treatment increased and/or lack of efficacy appeared.

The choice of the TNFα inhibitor was an opinion-based decision of the treating ophthalmologist and rheumatologist in collaboration and on the basis on drug availability at their center at the date of starting the anti-TNFα therapy.

Before each infliximab infusion, and every 30–45 days for adalimumab, children received a routine assessment consisting of a general physical examination, laboratory evaluation with renal and liver function tests, complete blood cell count and inflammation parameters, and a complete ophthalmologic evaluation, including best-corrected visual acuity on Snellen eye charts and slit-lamp examination, which was performed at study enrollment and according to the degree of activity thereafter. Once uveitis achieved remission, children underwent an ophthalmologic evaluation at each assessment or otherwise on clinical demand, as needed.

The exact same protocol was applied in the 3 centers. Approval was obtained by each local ethics committee. Parents or guardians gave their informed consent.

Patients. All of the patients in this series were recruited from the Paediatric Rheumatology Units in Florence, Brescia, and Trieste from June 2006 to November 2008.

During the same period of the study, our centers were following a total of 164 pediatric patients with chronic uveitis (112 females, 52 males, median age 6 years, range 3–18 years); 106 were associated with juvenile idiopathic arthritis (JIA), 7 with Behçet's disease, 1 with early-onset sarcoidosis, and 8 with other connective tissue diseases (systemic lupus erythematosus or mixed connective tissue disease), while the other 42 had idiopathic uveitis.

Thirty-three patients (22 females, 11 males, median age 9.2 years, range 5.2–13.8 years) resulted in being eligible for the study and were enrolled; 21 were recruited in Florence, 9 in Trieste, and 3 in Brescia.

In 25 of 33 children, active uveitis was associated with an underlying autoimmune disease: 22 JIA (11 oligoarticular, 7 extended oligoarticular, and 4 rheumatoid factor–negative polyarticular), 1 early-onset sarcoidosis, and 2 Behçet's disease. The other 8 children had idiopathic uveitis. Among 11 of 25 patients with secondary uveitis at enrollment, the associated underlying disease was active despite concomitant medications, while the remaining 14 patients were in remission on therapy with regard to the associated disease, but not to uveitis.

Before anti-TNFα treatments, all of the children had presented with active uveitis: 42 of 66 involved eyes, despite treatment with MTX at the dosage of 15 mg/m^2/week (n = 21), CSA at the dosage of 3 mg/kg/day (n = 8), and the combined administration of MTX and CSA (n = 4).

Three children with JIA in articular remission receiving etanercept (0.4 mg/kg twice a week) experienced uveitis while on this treatment: due to its refractory course, a 3-month trial of concomitant MTX therapy was added, but it resulted in being ineffective; therefore, concomitant therapy was stopped and they were eligible for the study.

Due to active uveitis along with topical steroids during the acute phase, all of the children were also receiving oral prednisone (1–2 mg/kg/day) at stable doses for at least 6 weeks (range 45–55 days).

Main outcome measures. Absence or recurrence rate of uveitis throughout the study period, visual acuity pre– and post–anti-TNFα treatment, tapering of steroid medication, and safety of administered drugs were recorded.

In order to compare their potential long-lasting effect on maintaining remission, the primary outcome was to assess, once remission was achieved, the time of a first relapse during treatment. In addition, secondary outcomes were to compare, once anti-TNFα treatment was started, time to uveitis remission, time to steroid discontinuation, and the number of uveitis relapses.

Anterior chamber cells and flare were graded according to the Standardization of Uveitis Nomenclature Working Group grading schemes for anterior chamber cells and flare criteria (14). Intraocular inflammation was considered "active" or uncontrolled if the inflammatory activity was grade $\geq$1+ at any examination.

Uveitis was defined as improved, and adalimumab or infliximab as successful, when its activity decreased by 2 steps in the level of inflammation (anterior chamber cells and/or vitreous haze) or decreased to grade 0. For assessing visual acuity, Snellen charts were used and "normal" acuity was defined as at least a best-corrected visual acuity of 20/25 (0.8 in a decimal scale = 0.10 in a logMAR format). "Improved" visual acuity was defined as a doubling of the visual angle (converted into a logMAR format) in at least 1 eye. Conversely, "worsened" visual acuity was defined as a halving of the visual angle at a logMAR format from baseline in at least 1 eye (corresponding to an increase or decrease of 3 lines on a decimal scale with a logarithmic chart) (15).

Statistical analysis. All of the results are expressed as the mean ± SD or median. Mann-Whitney U test, Wilcoxon's signed rank test for paired samples, chi-square tests, and Fisher's exact test, when appropriate, were used to compare data.

An a priori power analysis was completed using the G Power program (16). Two-tailed *P* values were employed. Considering current data of refractory uveitis in children, a large expected difference was estimated for the sample: the effect size F = 0.40, as per Cohen (17). In addition, power was set at 0.95, meaning there would be a 95% probability of reaching statistical significance if the obtained differences were truly present in the population. Results from the power analysis showed that 32 participants, 16 for each arm, in all groups combined would be required.

The following data, entered into a customized uveitis database, were considered as variables for correlations and as covariates for the survival curves: age at the study entry/age at the initiation of anti-TNFα therapy, sex, associated autoimmune disease, disease duration, age at uveitis onset, uveitis duration, active uveitis duration, time interval between the uveitis onset and the initiation of anti-TNFα, drug therapy administration (number and frequency), concomitant medications, previous cumulative corticosteroid dose and its duration, previous disease-modifying antirheumatic drug treatment duration, number of previous flares, number of patients with eye complications due to chronic uveitis (including glaucoma, synechia, band keratopathy, cystoid macular edema, vitreitis, and cataract), and followup time.

Before each eligible subject was recruited, an inclusion criteria second revision was performed by the Florence center, which acted as study coordinator and data management.

Pearson's and Spearman's correlation tests were used to determine correlation coefficients for different variables. In order to identify predictors of outcome, Cox regression model and Kaplan-Meier curves were constructed, each 1 at the mean of the covariates reported above. Nonparametric tests were used, where necessary, due to the small size of our groups and to the skewness of our data. Levels of *P* values less than 0.05 were considered statistically significant. All analyses were performed with the SPSS package for Windows, version 13.0.

RESULTS

Sixteen children (10 females, 6 males), 12 affected by JIA, 3 by idiopathic uveitis, and 1 by Behçet's disease, were recruited in the adalimumab cohort. Seventeen children (10 females, 7 males), of whom 10 were affected by JIA, 5 by idiopathic uveitis, 1 by early-onset sarcoidosis, and 1 by Behçet's disease, were enrolled in the infliximab group.

As reported in Table 1, demographic information and other reported variables in the statistical analysis section did not differ between the 2 groups.

No patient in the infliximab group had previously received adalimumab, and vice versa. The total median followup time receiving treatment was significantly higher in the infliximab group than in the adalimumab group (31 months, range 18–40 months versus 22 months, range 14–36 months; $P = 0.001$).

During the first year of treatment after starting anti-TNFα therapy, 31 of 33 children achieved complete remission: 15 of 16 receiving adalimumab over a median period of 12 weeks (range 8–16 weeks) and 16 of 17 receiving infliximab over a median period of 10 weeks (range 6–18 weeks; not significant). In 2 patients, both with JIA, the anti-TNFα therapy (1 receiving adalimumab and 1 receiving infliximab) was not able to control eye inflammation during the first year of treatment; therefore, they never achieved remission and were considered "nonresponders." They therefore resulted in being eligible for the inclusion criteria (refractory uveitis), but not for our outcome measures (absence or recurrence of uveitis), and therefore were excluded from the long-term survival analysis.

In regard to our primary outcome measure, at the mean of the abovementioned covariates, including the total length of followup time of the 2 cohorts, Cox regression analysis showed a higher probability of uveitis remission on adalimumab therapy than infliximab therapy during the time of treatment (log-rank, Mantel-Cox $\chi^2 = 6.83$, $P <$

Table 1. Comparison of variables for correlations and as covariates for the survival curves in 33 children with refractory chronic uveitis receiving adalimumab and receiving infliximab*

	Adalimumab (n = 16)	Infliximab (n = 17)	*P*
Age, years	8.4 (6.4, 12.3)	10.4 (5.2, 13.10)	0.19
Sex, female (%)/male	10 (62.5)/6	10 (58.8)/7	0.82
Age at onset of uveitis, years	5.4 (2.2, 11.4)	5.8 (2.4, 12.2)	0.43
Uveitis history duration, months	34 (10, 68)	29 (12, 84)	0.73
Children with associated autoimmune disease, no. (%)	13 (81.2)	12 (70.5)	0.68
No. (%) with active underlying disease	5 (31.2)	6 (35.3)	0.69
Age at onset of underlying disease, years	2.6 (1.2, 12.2)	2.4 (1.3, 12.5)	0.29
Disease duration at uveitis onset, months	8 (−13, 50)	10 (−16, 28)	0.74
Time interval between uveitis onset and anti-TNFα starting, months	48 (6, 75)	40 (12, 84)	0.71
Corticosteroids			
Oral dose, mg/kg	1.2 (0.25, 2)	1.3 (0.20, 2)	0.73
Previous oral cumulative dose, mg	960 (560, 3,400)	840 (300, 4,400)	0.82
Previous administration duration, months	9 (2, 16)	8 (3, 22)	0.85
Previous DMARD treatment duration, months	24 (8, 48)	21 (9, 66)	0.62
Active uveitis cumulative duration, months	6 (3, 11)	5 (3, 10)	0.42
No. of previous flares	4 (2, 6)	3 (2, 7)	0.54
No. (%) of patients with eye complications due to chronic uveitis	5 (31.2)	4 (23.5)	0.70

* Continuous variables are expressed as the median (range) unless otherwise indicated. Anti-TNFα = anti–tumor necrosis factor α; DMARD = disease-modifying antirheumatic drug.

0.001) (Figure 1). At 40 months of followup, which was the longest period common to the 2 groups, 9 (60%) of 15 children receiving adalimumab compared to 3 (18.8%) of 16 children receiving infliximab were still in remission on therapy (likelihood ratio 5.72, $P < 0.02$).

Considering the secondary outcomes, at the mean of the above reported covariates, survival Cox regression analysis did not show statistically significant differences between the 2 treatment groups with regard to time to remission and time to steroid discontinuation (Figures 2A and B). Twenty-six children (13 receiving infliximab and 13 receiving adalimumab) were able to stop steroid administration during the first 6 months from the start of anti-TNFα therapy; however, all 31 responders discontinued steroid administration before 1 year of treatment, with a median time of 3 months both for the adalimumab group (range 1–10 months) and the infliximab group (range 1–12 months).

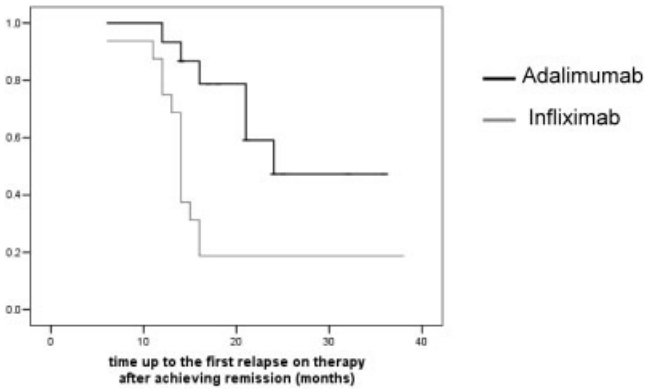

Figure 1. Survival curves of the time up to the first uveitis relapse on therapy after achieving remission (months) in the adalimumab group and in the infliximab group. On the y-axis, the probability of a patient being without relapse on anti–tumor necrosis factor α therapy is shown ($P = 0.001$).

In all 31 responders, no relapse of uveitis occurred during the first year of treatment, whereas before starting anti-TNFα therapy, the median number of relapses was 4 per year (range 2–6 per year) for adalimumab and 3 per year (range 2–7 per year) for infliximab. After the 1-year followup visit, among responders, 12 (80%) of 15 receiving adalimumab and 13 (82%) of 16 receiving infliximab met the criteria for improved visual acuity, corresponding to 19 (63%) of 30 eyes and 20 (62.5%) of 32 eyes, respectively (not significant). At the 1-year followup, the number of patients as well as the number of eyes within a "normal visual acuity" was significantly higher than before treatment both for the adalimumab (13 of 15 patients versus 3 of 15 patients; $P < 0.05$ and 21 of 30 eyes versus 9 of 30 eyes; $P < 0.03$) and infliximab groups (14 of 16 patients versus 3 of 16 patients; $P < 0.05$ and 25 of 32 eyes versus 9 of 32 eyes; $P < 0.02$). However, at 1 year of treatment, no significant differences were detected between the 2 treatment arms. None of the patients were amblyopic and refractive errors were corrected by means of glasses or contact lenses. All recorded variations in best-corrected visual acuity were therefore related to disease activity and no clearance of media was recorded.

Among children who relapsed, at 40 months of followup, the median number of relapses resulted as statistically significantly higher in the infliximab group than in the adalimumab group (3, range 1–5 versus 1, range 1–3; $P < 0.001$). At 40 months of followup, the median number of relapses per year receiving infliximab did not show a statistically significant difference than before infliximab (3, range 1–5 versus 3, range 2–7; not significant); on the

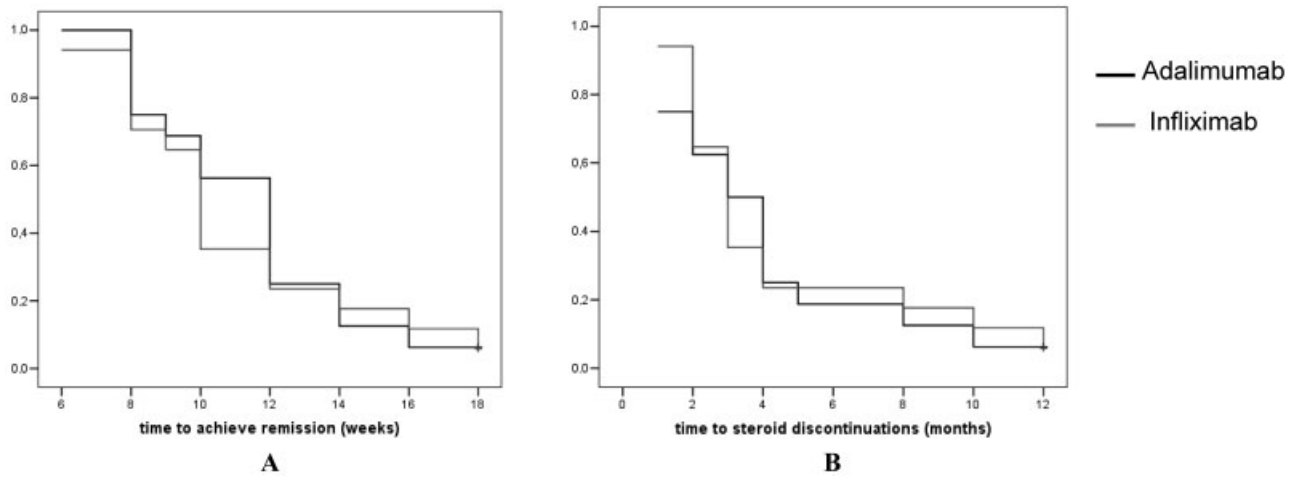

Figure 2. **A**, Survival curves of the time to achieve ocular activity remission (weeks) in the adalimumab group and in the infliximab group. On the y-axis, the probability of a patient being with active uveitis on anti–tumor necrosis factor α therapy is shown ($P = 0.83$). **B**, Survival curves of the time to steroid discontinuation (months) in the adalimumab group and in the infliximab group. On the y-axis, the probability of a patient being on steroid treatment is shown ($P = 0.71$).

contrary, the median number of relapses per year receiving adalimumab resulted as significantly lower than before treatment (1, range 1–3 versus 4, range 2–6; $P < 0.001$).

The total number of relapses during followup, limiting the analysis to a 40-month total period, correlated with the duration of infliximab treatment ($r_s = 0.85$, $P < 0.003$), but not with adalimumab treatment ($P = 0.81$).

In addition, we performed a subgroup analysis limited just to children with JIA with regard to our primary and secondary outcomes, and we obtained the same statistical results. Cox regression analysis showed a higher probability of uveitis remission on adalimumab therapy during the time of treatment entered for each cohort (log-rank, Mantel-Cox $\chi^2 = 4.12$, $P < 0.03$); at 20 months of followup, which was the longest period common to the 2 groups, 7 (63.6%) of 11 children receiving adalimumab compared to 1 (11.1%) of 9 children receiving infliximab were still in remission on therapy (likelihood ratio 4.24, $P < 0.02$). Again, we did not observe any statistical differences between the 2 groups with regard to the time to uveitis remission and the time to steroid discontinuation.

During the study period, 3 children with JIA developed a concomitant flare of arthritis associated with eye relapse, achieving a complete joint remission soon after the subsequent infliximab infusion in 2 children and after 3 adalimumab doses in the third patient.

Four patients developed complications attributable to infliximab, and 1 had to discontinue treatment. Two children experienced 1 episode of leukopenia, and in another, liver enzymes increased 3-fold; both of these adverse events were transient and they disappeared before the following infusion without the need to stop therapy. At the thirteenth infusion, 1 patient exhibited a severe infusion reaction (rash, hypotension, and respiratory distress) and stopped the therapy. Among adalimumab patients, 5 reported pain/burning/discomfort at the injection site, with concomitant local reaction in 2. No severe reaction requiring drug discontinuation and no significant laboratory abnormalities occurred.

DISCUSSION

Even if limited to a relatively small group, this comparative cohort study suggests that adalimumab is more efficacious than infliximab in a 3-year period of treatment of sight-threatening childhood uveitis, with regard to time of the first flare, once remission has been achieved.

To our knowledge, RCTs comparing adalimumab versus infliximab have not been published to date, and our study represents the first prospective cohort comparative study on this topic.

Starting with a superiority study design, we assumed that the null hypothesis (H = 0) is true; therefore, we assumed that there were not differences in efficacy and safety between these 2 anti-TNFα strategies in treating childhood chronic uveitis.

Our analysis indeed seems to accept the experimental hypothesis, suggesting that adalimumab during the first year of treatment has the same efficacy as infliximab, but during a longer followup shows a higher probability of maintaining remission. If our results are duplicated in a larger cohort, the evidence of this drug comparison on remission duration will reach a level IIb, converse of what is currently known on this topic (evidence level III). Therefore, when facing childhood-refractory chronic uveitis in clinical practice, the therapeutic strategy could be assessed using an evidence-based choice; with the same rate of efficacy but with a longer remission duration, it would be preferable to choose a drug that is easier to manage (adalimumab) than a drug that rather requires intravenous administration and hospitalization (infliximab). This strategy would result in better patient compliance and in a longer therapeutic efficacy.

Before drawing firm conclusions from our results, some caveats have to be discussed and considered. First, due to the rarity of the disease (refractory childhood chronic uveitis), the small sample size limits our study results. In addition, the inherent selection bias of 3 tertiary referral centers must be taken into account, and children enrolled

represent a heterogeneous population, with possible variable responses to treatment. The heterogeneity of the sample cohort, with regard to the underlying disease, might also affect the results of our study; however, we also reported a subcohort analysis, limited to the JIA children only, showing the same statistical results for efficacy, steroid sparing, and rate of recurrence at followup.

Notably, another shortcoming of our study is the type of treatment assignment used; it was not randomly assigned but chosen based on current knowledge of anti-TNFα treatment in childhood chronic uveitis and drug availability: an evidence level III, which means expert opinion, clinical experience, or descriptive study.

Even if prospective, the present study was not an RCT, and we perfectly recognize the scientific strength of an RCT versus a comparative cohort study. We have considered this topic during the study design formulation, but at this time, due to the actual knowledge on childhood chronic uveitis, we have also considered performing in advance an open-label pilot study as a prerequisite, since there was little evidence coming from the current literature to perform a double-blinded randomization in children, especially when dealing with this sight-treating and potentially disabling disease. In addition, an evidence level IIb could be better than actual knowledge and could be the basis for the study design of a more extensive and complete multicenter RCT on this topic.

However, our study is a multicenter study coming from 3 different units, and this strategy can in part reduce the bias due to a "subjective" decision: a supposedly better drug for more severely affected patients. In addition, because we have enrolled just "refractory uveitis," we have also considered that our study population is a "selected population," thus potentially inferring data through a selection bias; we thought to minimize this effect bias by performing statistical comparisons as much as possible, due to the sample size, in homogenous cohorts.

With regard to the long-term remission, the longer followup treatment period in the infliximab group when compared to the adalimumab group could affect the data, resulting in a nonhomogenous comparison; however, it has been considered as a covariate for the survival curves, therefore overweighting its potential effect size. The analysis was moreover limited to the 40-month followup, which was the longest period common to the 2 groups; moreover, as shown in Figure 2, the number of subjects in remission had a higher result in the adalimumab group already before the 20-month period.

Infliximab has been found to be effective as a short-term immunosuppressive agent in noninfectious uveitis in childhood, with increasing frequency in JIA-associated uveitis and in Behçet's disease (3,18–22). Nonetheless, its efficacy seems to wane over time, as we recently reported in a prospective case series of 15 children with childhood chronic uveitis followed for a period of 2 years (12), and as data from this prospective multicenter cohort seem to confirm. In agreement with these data, Tugal-Tutkun et al reviewed the medical records of 20 children with uveitis who had been treated with infliximab; although all of the patients received concomitant immunosuppressive therapy, 4 patients showed uveitis reactivation due to loss of efficacy at 10–36 months of infliximab therapy (23). Notably, higher doses of infliximab have then also been used in treating refractory uveitis in long-term followup. Kahn et al (5) used 10 to 20 mg/kg at each infusion and Rajaraman et al (24) similarly obtained a good control of ocular inflammation over a 48-week period, increasing the dose to 18 mg/kg. Recently, Ardoin et al (25) reported that a median maintenance infliximab dose of 8.2 mg/kg was necessary in order to control uveitis over a 26-month followup period.

Conversely, Suhler et al, in an open-label 2-year prospective study on infliximab, reported a high rate of discontinuation of almost 65% because of the occurrence of significant adverse events, inefficacy, and patient compliance (26).

To date, no placebo RCTs have been performed in order to assess the efficacy of infliximab in pediatric uveitis.

Adalimumab has been suggested to be the most efficacious TNFα blocker for childhood uveitis (11), even though larger trials are needed to confirm this hypothesis. Vazquez-Cobian et al have described 14 children with uveitis (9 JIA-associated and 5 idiopathic) treated with adalimumab for an average of 18.1 months: reduced inflammation was reported in 21 (80.8%) of 26 eyes, a stable situation in 4 eyes (15.4%), and worsening in 1 eye (3.8%). No adverse effects occurred (9). As in our series, Biester et al (10) found that adalimumab was effective in 10 of 16 patients with JIA-related uveitis and in 16 of 18 children with idiopathic uveitis, with no acute side effects or a high incidence of infections. In 15 children, it also allowed the discontinuation of systemic corticosteroids, and in the remaining 3 patients a reduction to low doses was achieved. Tynjälä et al recently reported their experience of 20 children with JIA and chronic uveitis treated with adalimumab (27). Seventeen patients (85%) had polyarticular JIA and 19 (95%) had previously received another anti-TNFα agent. The mean duration of adalimumab therapy was 18.7 months. Seven patients (35%) showed improved activity, 1 (5%) showed worsening activity, and in 12 (60%), no change was observed. Those with improved activity were younger and had shorter disease duration. The mean number of flares per year decreased from 1.9 to 1.4 during adalimumab treatment. Adverse events were not observed. Seven patients discontinued adalimumab during followup: 6 because of inefficacy and 1 because of remission of uveitis (27).

In agreement with the aforementioned studies, our data suggest that adalimumab is rapidly effective and well tolerated, representing an appealing steroid-sparing agent with no significant adverse events, irrespective of the underlying associated disease.

As far as we know, this is the first prospective comparative study between these 2 anti-TNFα agents in childhood chronic uveitis, showing for adalimumab superior activity in maintaining remission over a relatively long-term treatment period. Of note, converse to most of the previously published studies, our data came from a prospective, rather than retrospective, comparative case series, representing the longest prospective followup available study for adalimumab therapy in childhood-refractory chronic uveitis.

However, additional long-term prospective case series are needed to better understand the correct anti-TNFα strategy for childhood-refractory chronic noninfectious uveitis, and a randomized clinical trial might be advocated on this topic. A recently published case series suggested that in case of refractory uveitis with loss of initial clinical response to 1 biologic agent, switching to another agent can restore control of intraocular inflammation and may help to control systemic symptoms (28). Accordingly, Biester et al also reported favorable results in each "direction" among the current available anti-TNFα options: an achievement and maintenance of remission of ocular inflammation on adalimumab, when infliximab or etanercept were not effective or not tolerated, but also efficacy of etanercept or infliximab in case of adalimumab failure, or fair and weak control of ocular disease (10).

In conclusion, even if limited to a small group, this comparative cohort study on anti-TNFα treatment for sight-threatening childhood uveitis suggests that adalimumab is as efficacious as infliximab in a short-term period, but maintains in remission for a longer period and with a higher rate. Prospective RCTs are needed to verify this finding.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Simonini had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Simonini, Taddio, Cattalini, Caputo, De Libero, Lepore.

Acquisition of data. Simonini, Taddio, Cattalini, Caputo, De Libero, Naviglio, Bresci, Lorusso, Lepore, Cimaz.

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