Concise Report

Loss of efficacy during long-term infliximab therapy for sight-threatening childhood uveitis

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Objective. To describe efficacy and safety of infliximab in the treatment of childhood chronic uveitis during a long-term follow-up.

Methods. Fifteen patients (median age 12 yrs, range 5–21 yrs) with chronic uveitis were enrolled. Before infliximab treatment, children had presented active uveitis despite treatment with MTX and/or CSA. All were also receiving oral prednisone (1–2 mg/kg/day) for at least 1 month. Infliximab (5 mg/kg) was administered at weeks 0, 2, 6 and then every 6–8 weeks. Later on, in patients enrolled in Florence the administration interval was progressively increased up to 10 weeks if uveitis did not flare, whilst in children from Padua the scheduled infusion rate was maintained every 6 weeks. Absence or recurrence rate of uveitis up to the last visit was recorded.

Results. Median follow-up on treatment was 30 months (range 16–38 months), median number of infusions 22 (range 11–30). During the first year, 13/15 children achieved a complete remission over a median period of 10 weeks, but all relapsed thereafter. The probability of a first relapse was correlated to length of treatment, once remission was achieved (P < 0.03). The total number of relapses correlated with the duration of treatment (r = 0.81; P < 0.002) and with the total number of infusions (r = 0.83; P < 0.001). The total number of relapses on treatment at last follow-up was not significantly different between the two centres.

Conclusions. Even if limited to a small group, infliximab appears to be an effective treatment for uveitis in children, but its efficacy seems to wane over time.

KEY WORDS: Children, Chronic uveitis, Infliximab.

Introduction

Non-infectious uveitis in childhood is a relatively uncommon, but serious disease, with the potential for significant long-term complications and eventually blindness [1].

Although frequently associated with an underlying systemic disease, e.g. juvenile idiopathic arthritis (JIA), a significant number of cases do not show any associated sign or symptom, and are labelled as idiopathic. In general, it is thought that non-infectious uveitis represents an immune-mediated disease and cell-mediated immunity is advocated in its pathogenesis, providing a rationale for immunosuppressive such as corticosteroid treatment [2].

To control signs and symptoms of ocular inflammation, the mainstay of initial therapy relies mainly on local and/or systemic corticosteroids, according to the severity of the disease [3]. Usually, refractory uveitis requires early and aggressive treatment with immunomodulatory therapy, in order to preserve visual acuity and to prevent the significant morbidity of chronic administration of steroids. Several immunosuppressive steroid-sparing agents, such as MTX, CSA and AZA, have been tried with variable success and each has significant potential toxicity. However, up to now the experience consists largely on case reports and small case series, while prospective and randomized studies are rare. Indeed, none of these drugs have been demonstrated to be effective in controlled studies [4].

Following evidences of TNF-α as significant player in the development of uveitis, recently TNF-α blocking agents have been used to treat non-infectious, chronic and refractory uveitides, in adulthood as well as in childhood [5–11].

Aim of our study was to evaluate the efficacy and safety of infliximab in the treatment of childhood chronic uveitis during a long-term follow-up, over 1 yr of treatment. In particular, our primary outcome measure was to assess, once achieved remission, the time to a first uveitis relapse over long-term treatment with infliximab, in order to address its potential long-lasting effect on maintaining remission.

Materials and methods

Study design

Prospective, comparative case series of paediatric patients with refractory uveitis were treated with infliximab for a study period of over 1 yr in two tertiary paediatric rheumatology centres (Anna Meyer Children’s Hospital, Florence and University Hospital, Padua, Italy).

Inclusion criteria

To be considered for enrolment in this study, patients were required to have vision threatening non-infectious uveitis that was refractory to therapy with systemic corticosteroids and at least one other immunosuppressive medication, or to be intolerant to such therapy.

‘Refractory’ was considered as persistently active uveitis for at least 3 months despite the systemic steroids and immunosuppressive treatment (MTX and/or CSA). In all cases disease onset occurred before the 16th birthday.

Study and treatment protocol

Before enrolment, all patients provided a detailed medical history and underwent a complete rheumatological and ophthalmological examination; in particular, all children were required to undergo a tuberculin protein purified derivative skin test and chest radiograph before starting infliximab.

Footnotes

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After stopping the previous immunosuppressive therapy (except corticosteroids), children initially received infliximab infusions at the dose of 5 mg/kg at weeks 0, 2, 6 and then every 6–8 weeks for at least 1 yr (range 12–14 months). MTX treatment at very low dose (5 mg/weekly) was maintained and/or added to prevent the formation of anti-infliximab autoantibodies. Later on, in patients enrolled in Florence, the administration interval was progressively increased up to 10 weeks if uveitis did not relapse, whilst in children from Padua the scheduled infusion rate was maintained every 6 weeks.

Patients received a general physical examination and laboratory evaluation before each infusion; pre-infusion blood tests included renal and liver function tests, complete blood count and inflammation parameters (ESR, CRP).

A complete ophthalmologic evaluation, including best corrected visual acuity (BCVA) on Snellen eye charts and slit lamp examination, was performed at study enrolment and according to the degree of activity thereafter. Once uveitis achieved remission, children underwent an ophthalmologic evaluation before each infusion or otherwise on clinical demand when needed.

Approval was obtained by the ethics committees of hospital in Florence and in Padua; parents or guardians gave informed consent.

**Patients**

All patients in this series were recruited from the Pediatric Rheumatology Units in Florence and Padua from June 2005 to June 2007. During the same period of the study, our two centres were following a total of 119 pediatric patients with chronic uveitis (84 females, 35 males; median age 6 yrs, range 2–21 yrs); 81 were associated with JIA, 4 with Behçet’s disease, 1 with early onset sarcoidosis, 5 with other CTDs (SLE or MCTD), while the other 28 had idiopathic uveitis. Fifteen patients (10 females, 5 males; median age 12 yrs, range 5–21 yrs) resulted eligible for the study and were enrolled: eight were recruited in Florence, seven in Padua. In 12 out of 15 children, uveitis was associated with an underlying autoimmune disease: 10 JIA (five oligoarticular, three extended oligoarticular, two RF-negative polyarticular), one early-onset sarcoidosis, one Behçet’s disease. The other three children had idiopathic uveitis.

Among 5/12 patients with secondary uveitis, at enrolment, the associated disease was active despite the concomitant medications, while in the remaining seven it was active in remission on therapy. Before infliximab treatment, all children had presented active uveitis: 19/30 involved eyes, despite treatment with MTX at the dose of 15 mg/m²/weekly (n = 10), CSA at the dose of 3 mg/kg/day (n = 3) and combined administration of MTX and CSA (n = 2).

Due to active uveitis, all were also receiving oral prednisone (1–2 mg/kg/day) and topical steroids, for a duration of at least 1 month (range 30–45 days).

**Main outcome measures**

Absence or recurrence rate of uveitis throughout the study period, visual acuity pre- and post-infliximab, tapering of steroid medication and safety of infliximab were recorded.

Anterior chamber cells and flare were graded according to the SUN Working Group grading schemes for anterior chamber cells and flare criteria [12]. Intraocular inflammation was considered ‘active’ or uncontrolled if the inflammatory activity was grade ≥1+ at any examination. Uveitis was defined as improved, and infliximab as successful when patient with active uveitis at the onset of treatment, achieved on therapy improved activity, defined as two-step decrease in level of inflammation (anterior chamber cells and/or vitreous haze) or decrease to grade 0.

For assessing visual acuity, Snellen charts have been used and ‘normal’ acuity was defined at least as BCVA 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 in a LogMAR format) in at least one eye. Conversely, ‘worsen’ visual acuity was defined as a halving of the visual angle at a LogMAR format from baseline in at least one eye (corresponding to an increase or decrease of three lines at a decimal scale with a logarithmic chart) [13].

**Statistical analysis**

All results are expressed as mean or median ± s.d. Mann–Whitney U-test, Wilcoxon signed-rank test for paired samples and Fisher’s exact test, when appropriate, were used to compare data. Pearson and Spearman correlation tests were used to determine correlation coefficients for different variables (age, gender, associated autoimmune disease, disease duration, age at uveitis onset, age at initiation of therapy with infliximab, administration rate, number of infusions, follow-up time). Cox regression model and Kaplan–Meier curves were constructed, in order to identify predictors of outcome. Non-parametric tests were used, where necessary, due to the small size of our groups and to the skewness of our data. Levels of \( P < 0.05 \) were considered statistically significant. All analyses were performed on SPSS package for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA).

**Results**

The demographic information for enrolled patients who responded to treatment as well as their main outcome measures are summarized in Table 1.

Median follow-up time of treatment was 30 months (range 16–38 months), median number of infusions 22 (range 11–30). During the first year of treatment, 13/15 children achieved a complete remission on infliximab over a median period of 10 weeks (range 6–16 weeks) after starting therapy. In two patients, infliximab was not able to control eye inflammation during the first year of treatment, thus never entered in remission and were therefore considered ‘non-responders’.

Eleven (85%) children were able to taper systemic steroid therapy by at least 50% during the first 2 months on therapy (1–3 months), and all responders stopped steroid administration during the first 3 months (range 2–5) from study entry.

No relapse of uveitis occurred in these 13 patients during the first year, while before starting infliximab the median number of relapses was 4/yr (range 2–6). After the 1-yr follow-up visit, among responders, 10/13 (77%) children met the criteria for improved visual acuity, corresponding to 16/26 (62%) eyes. At that time, the number of patients as well as the number of eyes within a ‘normal visual acuity’ was significantly higher than before infliximab therapy (patients 11/13 vs 2/13, \( P < 0.03 \); eyes 18/23 vs 7/26, \( P < 0.03 \)).

None of the patient was amblyopic and refractive errors were corrected by means of spectacles or contact lenses. All recorded variations in BCVA were therefore related to disease activity and no clearance of media was recorded.

The two children who never achieved remission, thus being non-responders to infliximab, resulted being eligible for the inclusion criteria (refractory uveitis) but not for our principal outcome measure (absence or recurrence of uveitis) and therefore were excluded from the long-term survival analysis. All 13 responder children relapsed after the first year of infliximab infusions. At the first relapse of uveitis, median follow-up on treatment was 15 months (range 12–23) and the median number of infusions was 12 (range 10–18).

Figure 1 shows the survival curve of our patients up to the first uveitis relapse. Cox regression analysis showed that the probability of a first episode of relapse was correlated to length of treatment, thus the time from onset of infliximab treatment was the only identified predictor of a new uveitis relapse, once achieving the remission on therapy (\( P < 0.03 \)).
The total number of relapses during follow-up, up to June 2007, showed a statistically significant correlation with the time from onset of infliximab treatment (r = 0.81; P < 0.002) and with the total number of infusions (r = 0.83; P < 0.001). At the last follow-up, the median number of relapses for each child was 3 (range 2–4). The total number of relapses on treatment at the last follow-up was not significantly different between the two centres (Florence: median 3, range 2–4 vs Padua: median 4, range 3–5) despite the different dosing intervals. During the study period, only two children with JIA developed concomitant flare of arthritis associated with eye relapse, achieving a complete joint remission soon after the successive infliximab infusion.

Three patients developed complications attributable to infliximab, and one of them had to discontinue treatment. One child experienced one episode of leucopenia, and in another liver enzymes increased by 3-fold; both these adverse events were experienced one episode of leucopenia, and in another liver enzymes increased by 3-fold; both these adverse events were associated with eye relapse, achieving a complete joint remission soon after the successive infliximab infusion.

Discussion

In agreement with previous studies [7–10, 14–17], our data confirm the safety and efficacy of infliximab as a treatment of choice in children with refractory uveitides. The efficacy of this treatment seems independent from the underlying associated autoimmune disease, if present. However, our article reports the progressive loss of efficacy of infliximab for sight-threatening uveitis [7].

Richards et al. [17] demonstrated the improvement in visual acuity and degree of inflammation on infliximab in 21 and 13 children with chronic uveitis associated with JIA, respectively. However, our study demonstrated a good control of intraocular inflammation with infliximab in six children with idiopathic uveitis (n = 1), JRA (n = 3), idiopathic retinal vasculitis (n = 1) and bilateral pars planitis (n = 1). Kahn et al. [7] described 17 children, (10 with JIA, 2 with sarcoidosis, 3 with idiopathic uveitis, and 2 with Vogt–Koyanagi–Harada syndrome), who were given high doses of infliximab and showed a dramatic and rapid response of their uveitis [7].

Saurenmann et al. [9] reported the beneficial effect of infliximab in 13 children with uveitis (two idiopathic, one Behcet’s, one sarcoidosis and nine JIA), underlying the better clinical response than with etanercept, even if in an uncontrolled study.

In 2007, Tynjala et al. [15] and Gallagher et al. [10] demonstrated the improvement in visual acuity and degree of inflammation on infliximab in 21 and 13 children with chronic uveitis associated with JIA, respectively.

Similar results with regard to infliximab efficacy in treating childhood uveitis were also obtained in retrospective case series by Richards et al. [16], Sharma et al. [17] and Ardoit et al. [18].

As in our series, the aforementioned studies agree that infliximab was rapidly effective and well tolerated, and it was an appealing steroid-sparing agent, with no significant and serious adverse events in children with refractory uveitides, irrespectively from the underlying associated disease, if present.

However, we have shown that after 1yr on infliximab, its efficacy on childhood uveitides seem to wane: by 12–14 months of therapy, the probability of a uveitis relapse is quite high and at
16 months of follow-up all our patients but one had relapsed. The number of flares did not seem to be related to the interval of administration, but rather to the total duration of treatment. We are not able to explain this phenomenon, but cannot exclude that anti-infliximab antibodies might develop despite the concurrent administration of MTX, and that they could be responsible for this late partial loss of efficacy. We did not measure anti-infliximab antibodies in our series.

The different schedule of treatment might also be advocated to explain the progressive loss of efficacy; however, in our series we did not observe any difference with regard to number of relapses in two groups of patients treated with different protocols (longer or shorter intervals between infusions).

Notably, another shortcoming of our study is that it does not examine the efficacy of infliximab since there is no comparison group. It could be hypothesized that relapse occurs because the maintenance regimen of infliximab and low-dose MTX is insufficient rather than infliximab losing its efficacy. The treatment implications of these considerations could be rather different as one would suggest replacing infliximab and the other would suggest supplementing it with more effective adjunctive treatment.

Rajaraman et al. [14] observed a maintained good control of ocular inflammation over a 48-week follow-up at 4- to 8-week intervals, but at increased dose up to 18 mg/kg. High-doses of infliximab (10–20 mg/kg) were also effective in Kahn’s series [7]. The beneficial effect in the 3-yr retrospective study by Saurenmann et al. [9] was observed with infliximab infusions at 3–10 mg/kg given every 4–8 weeks, whilst in the retrospective series by Gallagher et al. [10] the infliximab infusions (range 100–700 mg) were continued at 4- to 8-week intervals for an average duration of treatment of 16 months. The retrospective study from Finland [15] showed an improved ophthalmological outcome in one-third of the patients at the 24-month end-point evaluation with 3–6 mg/kg doses, given every 4–8 weeks. In the recent retrospective case series reported by Ardoni et al. [18] median maintenance infliximab doses of 8.2 mg/kg, with a median interval infusion period of 5 weeks, were necessary to control uveitis in a 26-month follow-up period.

As far as we know, our study is the first where a progressive loss of efficacy of infliximab over >1 yr of treatment is documented. Of note, conversely to most of the previously published studies, our data came from a prospective, rather than retrospective, comparative case series and, as far as we know, with the longest prospective follow-up available for children.

As reported in recent papers [10, 19, 20] alternative biologic agents such as daclizumab or adalimumab seem to be promising alternatives as a valid appealing treatment in childhood refractory uveitis. We are also following this approach in our patients with childhood uveitis when infliximab loses its efficacy, also considering the fact that the other anti-TNF agent etanercept has not been shown to be efficacious in a controlled study [21].

In conclusion, even if limited to a small cohort, our data show that infliximab appears to be an effective treatment for uveitis in the short term, but its efficacy seems to wane over time. Alternative therapy for preserving visual acuity in children with refractory uveitis may be advocated.

Disclosure statement: The authors have declared no conflicts of interest.

References