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ORIGINAL ARTICLE

Tocilizumab as an Effective Treatment Option in Children with Refractory Intermediate and Panuveitis

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ABSTRACT

Purpose: To describe the results of tocilizumab treatment in children with refractory non-anterior uveitis.
Methods: A case series of seven children with refractory non-anterior uveitis (onset ≤16 years) with leakage on fluorescein angiogram (FA) were treated with tocilizumab intravenously every 4 weeks (eight mg/kg). Minimum follow-up was 6 months. Reported outcomes are changes in BCVA, central macular thickness (CMT) on OCT image, FA scores, dose of systemic steroids, complications and side effects.
Results: In all patients, there was an improvement of macular edema and capillary leakage on FA. The median FA score decreased from 14 (10–18) at baseline to 8 (2–9) after 6 months of treatment (p = .018). The CMT decreased from 321 (314–384) to 295 (255–312) (p = .043). BCVA improved in five eyes and worsened in one eye due to cataract. No systemic or ocular complications were reported.
Conclusion: Tocilizumab is an effective therapeutic option for reducing disease activity in children with refractory non-anterior uveitis.

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Pediatric; uveitis; inflammation; tocilizumab; treatment

Introduction

Pediatric uveitis is a very challenging condition to treat. It leads to irreversible visual impairment in up to one-third of the affected children.[1,2] Underlying etiology as well as treatment response varies widely in these patients. Corticosteroids have been traditionally used as the first-line treatment, but given their severe adverse effects (i.e. growth retardation and Cushing syndrome) choosing for immunomodulating treatment (IMT) like mycophenolate mofetil (MMF) or methotrexate (MTX) earlier in the disease course is widely accepted nowadays. However, also IMT is frequently not sufficient to control uveitis; more than half of the patients eventually need to start additionally with biologicals.[3] The therapeutic potential of adalimumab (TNF-α inhibitor) in adults with noninfectious uveitis and children with juvenile idiopathic arthritis (JIA) associated uveitis is well known.[4–8] However, caution should be kept in mind for TNF-α inhibitors as a treatment for intermediate uveitis (IU) due to a potentially increased risk of demyelinating disease of the central nerve system. [6] So there is an unmet need for additional effective treatment options in children with refractory IU and panuveitis dependent on chronic treatment with corticosteroids.

Tocilizumab (TCZ) is a recombinant humanized antibody directed against the IL-6 receptor. While the effectiveness of TCZ was established in the treatment of cystoid macula edema (CME) and JIA associated uveitis, there is still little known about its effect in pediatric noninfectious IU and panuveitis.[9–11] In this retrospective cohort, we describe the results of TCZ treatment in children with refractory IU and panuveitis.

Methods

This is a retrospective cohort of children with visual threatening idiopathic IU and panuveitis (onset before 16 years of age) with severe leakage on the fluorescein angiography (FA) and refractory to treatment with a combination of systemic corticosteroids, one or more IMT and TNF-α inhibitors (adalimumab) or with relative contraindications for TNF-α inhibitors see Table 1. All patients were treated with TCZ between 2016 and 2018 at the department of ophthalmology of the University Medical Center of Utrecht (n = 6) and St. RadboudUMC Nijmegen (n = 1), tertiary reference centers in The Netherlands. Parents and patients were aware of the use of an off-label drug and gave their consent. Uveitis was diagnosed by an ophthalmologist specialized in pediatric uveitis. Diagnosis of uveitis was made according to the criteria of the International Uveitis Study Group.[12] After screening of all patients by a pediatric rheumatologist, none of the patients had a related systemic auto-inflammatory or autoimmune disease.

All patients received 8 mg/kg TCZ intravenously (weight of all patients was above 30 kg) given every 4 weeks (second infusion after 2 weeks) in addition to IMT and systemic

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Table 1. Demographic characteristics of pediatric patients with intermediate and panuveitis treated with tocilizumab.

Case	Sex	Diagnosis	Age at diagnosis	Prior medication	interval uveitis-TCZ (years)	Total duration of follow up after initiation of TCZ (months)	Medication change			
							Baseline	6 months	12 months	Last follow up visit(6–24 months)
1	M	IU	5	Cortico; MMF; MTX; Cyclo; ADA	11.72	24	Cyclo 120mg; MMF 1500mg; Cortico 5mg EOD TCZ 8mg/kg	Cortico 5mg EOD	Cortico 5mg EOD	No cortico (24)
2	F	IU	4	Cortico; MMF; MTX; MA; ADA	7.87	24	Cortico10mg; MA 720mg; TCZ 8mg/kg	Cortico 10mg	Cortico 5mg	No cortico (24)
3	M	IU	3	Cortico; MMF; MTX; ADA	10.49	24	Cortico 5mg; MMF1200mg; TCZ 8mg/kg	Cortico 5mg EOD	Cortico 5mg EOD	Cortico 5mg EOD (24)
4	M	IU	9	Cortico; MMF	16.95	12	MMF 2000mg; TCZ 8mg/kg	No cortico	No cortico	No cortico (12)
5	M	IU	11	Cortico; MMF; MTX; MA; ADA	5.49	24	Cortico 10mg TCZ 8mg/kg	No cortico	No cortico	No cortico (24)
6	F	Pan	7	Cortico; MMF; MTX; ADA	3.36	12	Cortico 30mg; MMF 1500mg; TCZ 8mg/kg	Cortico 12.5mg	Cortico 12.5mg	Cortico 12.5mg (12)
7	F	Pan	6	Cortico; MTX; MMF	9.98	6	MMF; TCZ 8mg/kg	No cortico	No cortico	No cortico (6)

M, male; F, female; IU, intermediate uveitis; Pan, panuveitis; cortico, corticosteroids; MMF, Mycophenolate mofetil; MA, Mycophenolic acid; MTX, methotrexate; Cyclo, cyclosporin; ADA, Adalimumab; TCZ, tocilizumab; mg, milligram; EOD, every other day.

corticosteroids (Table 1). The minimum follow-up was 6 months.

Reported outcomes are changes in disease activity scored by anterior chamber cells according to Standardization of Uveitis Nomenclature (SUN) classification[12] and was graded by the ophthalmologist specialized in pediatric uveitis, central macular thickness (CMT) on optical coherence tomography (OCT) image and FA scores according to Angiography Scoring for Uveitis Working Group (ASUWOG).[13] Other outcomes are best corrected visual acuity (BCVA), dose of systemic corticosteroids and ocular and systemic complications and/or side effects.

Data are retrospectively collected from the electronic patient file at baseline, six and every following 6 months after start of treatment with TCZ. The data are presented in continuous or ordinal variables (BCVA, CMT on OCT image, FA score and dose of systemic corticosteroids). The eye with the highest FA score at baseline (worst eye) was used for analysis. One patient had poor vision in one eye (left) due to previous retinal detachment. Only the other eye (right eye) was used for the visual acuity analysis. Wilcoxon signed-rank test was applied for continuous and McNemar's Chi-square test for categorical variables. P-values below 0.05 were considered as statistically significant.

Results

In the period of 2016–2018, seven patients with bilateral refractory idiopathic IU (n = 5) and panuveitis (n = 2) were treated with TCZ after previous failure of corticosteroid and other traditional and anti-TNF-α immunosuppressive therapy. Two patients had a relative contraindication for TNF-α inhibitors, because of suspicion of neuritis and demyelination on MRI brain. Demographic and baseline characteristics of patients are reported in Table 1. The age at diagnosis ranged from three to 11 years. Complications of long-term corticosteroids use i.e. growth retardation and Cushing were reported in all patients. The previous immunosuppressive treatment consisted of methotrexate (n = 6), mycophenolate (n = 7), mycophenolic acid (n = 2), cyclosporine (n = 1) and adalimumab (n = 5). The interval between onset of uveitis and starting treatment with TCZ ranged between three and 11 years with median of 7.9 (interquartile range [IQR] 6.4–10.0) years (Table 1).

In all patients, there was a striking reduction in overall FA score from 14 (10–18) at baseline to 8 (2–9) after 6 months of treatment (p = .018) and 5 (1.50–6.75) after 12 months (p = .028). This was mostly due to reduction in macula edema and capillary leakage. There was a significant decrease of the CMT measurement on OCT image (Figures 1, 2 and Table 2). At baseline, three patients had intraretinal cysts shown on FA. In one of these patients, macular cysts were identifiable on the OCT image. The retinal alterations had disappeared in all three patients after 6 months of treatment. Retinal neovascularization at baseline was still present at the 12-month follow-up visit in one eye of one patient.

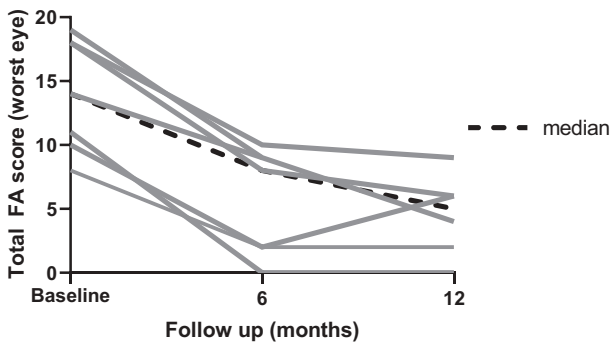

Figure 1. Total median fluorescein angiography score per case (worst eye) and the median total fluorescein angiography at baseline, 6-month and 12 -month follow-up.

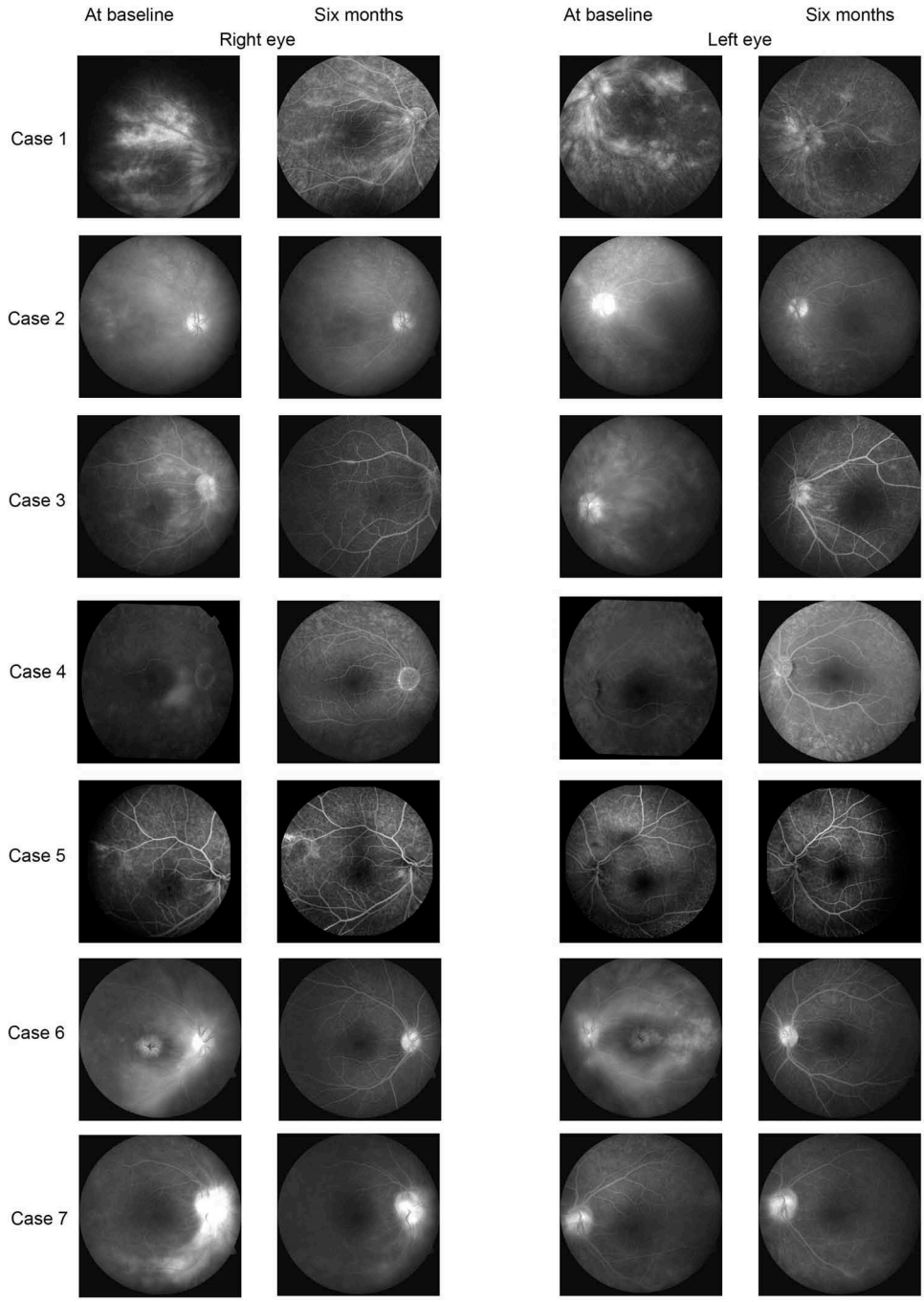

Figure 2. The two left columns show the fluorescein angiography of the right eye per case at baseline and after 6 months of treatment. The two right columns show the fluorescein angiography of the left eye per case at baseline and after 6 months of treatment.

Improvement of BCVA was observed in five (out of 13) eyes (two patients bilaterally), stabilization in seven eyes and worsened in one eye due to cataract (0.15 to 0.22 LogMAR) in a follow-up period of 6–12 months. The median BCVA, however, did not significantly change (Table 2). Cataract was present at baseline in five eyes of three patients with no change during follow-up.

In three out of five patients the dose of systemic corticosteroids could be ceased and reduced in two patients in the last follow-up visit (Table 2).

No systemic or ocular complications were reported during the follow-up period.

Discussion

This small case series shows that treatment with TCZ is successful in children with refractory IU and panuveitis who failed on TNF-α inhibitors or had a relative contra-indication for TNF- α inhibitors. In all patients, TCZ seems very effective to improve macular edema and capillary leakage on FA.

Approximately 94% of children with idiopathic uveitis need systemic steroids during the course of disease and more than 50% require IMT and biologicals.[3] TNF-α inhibitors showed to be effective in different forms of (childhood) uveitis.[4–8] They are, however, being given with caution in case

Table 2. Fluorescein angiography score, central macular thickness measurement on OCT image and best-corrected distance visual acuity of the eye with the highest FA score at baseline, 6 months and 12 months of follow up.

	Baseline *n* = 7	6 months *n* = 7	*P*-value[b]	12 months *n* = 6	*P*-value[b]
FA CME[a]	3 (1–4)	0 (0–1)	.017	0.5 (0–1.25)	.027
FA capillary leakage[a]	7.0 (6–10)	4.0 (0–7)	.017	2.5 (0.75–4.25)	.028
FA vasculitis[a]	2 (1–3)	1 (0–2)	.034	0 (0–0.5)	.056
FA optic disc leakage[a]	2 (0–3)	1 (0–2)	.034	1 (0–2)	.083
FA total score[a]	14 (10–18)	8 (2–9)	.018	5 (1.5–6.75)	.028
BCVA in LogMAR	0.15 (0.00–0.22)	0.05 (−0.08–0.22)	.786	0.02 (0.00–0.30)	.500
CMT in µm	321 (314–384)	295 (255–312)[c]	.043		

Data given as median (interquartile range). The eye with the highest FA score at baseline was used for analysis. FA, fluorescein angiography; CME, cystoid macula edema; BCVA, best-corrected distance visual acuity; LogMAR, logarithm of minimal angle of resolution; CMT, central macular thickness; µm, microns.
[a]FA scores as described by The Angiography Scoring for Uveitis Working Group.[13]
[b]*P*-values computed with Wilcoxon signed-rank test.
[c]Measurement after 9 months of treatment.

of traditional IMT failure because of reports on demyelination in patients with non-anterior uveitis. Therefore, in all patients with non-anterior uveitis, an MRI scan of the brain is recommended before starting TNF-α inhibitors. Two out of seven patients had white matter abnormalities on MRI preexistent to treatment. This was classified as a relative contraindication for TNF-α inhibitors. Five out of seven patients were treated with adalimumab with unsatisfactory results.

TCZ is emergently regarded and used as a valuable treatment option for JIA associated uveitis.[9–11] Additionally, TCZ in adults with non-anterior uveitis and refractory uveitis-related cystoid macula edema is well established.[14–21] The STOP-Uveitis Study demonstrated that monthly intravenous TCZ infusions significantly improved the visual, anatomic and inflammatory outcomes in patients with non-anterior uveitis with limited systemic and ocular adverse effects.[14] Comparable results were seen with sarilumab subcutaneous, another anti-IL-6 receptor, in adult uveitis.[22] Meanwhile data on the effectiveness and tolerance of TCZ in pediatric non-anterior uveitis are still lacking.

In our study, there was a striking improvement of disease activity and reduction of macular leakage on FA after 6 months of treatment with TCZ intravenously. This emphasizes the important role of regularly performed FA in evaluating treatment results.

A significant decrease in CMT measurement on OCT image was seen in our study. However, other studies which reported this effect, show a more substantial reduction[14,16,17,21-,22] This might be explained by the absence of macular cysts in most of our patients. None of the patients had any tractional component.

At present, it is unknown whether TCZ subcutaneously will have the same effect on uveitis activity but favorable results were reported with sarilumab subcutaneously.[22] Like in our study, corticosteroid-sparing effect of TCZ has been reported in many other studies.[14,15,17,18,20–22] This is an important aspect since in our cohort, all patients had unwanted steroid-related complications i.e. growth retardation, Cushing syndrome and osteoporosis at this young age.

Although favorable effect on vision after treatment with anti-IL-6 receptor has been reported, in our study, improvement in BCVA was observed in the minority of the eyes in our series (five of 13) within the follow-up.[14,16,17,,21,22] This can be explained by study design (children versus adults), the number of patients with CME and cataract development.

In the literature reported complications of TCZ are low absolute neutrophil counts, leukopenia and thrombocytopenia.[15,18] None of these were observed in our study. Conversely, in trials in patients with systemic juvenile idiopathic arthritis, 66-88% of patients had at least one adverse event.[23,24] This is probably related to systemic inflammatory condition and not comparable with our population.

The primary limitation of our study is its small sample size. However, uveitis is a rare entity and moreover, the clinical value for new therapies with less side effects in this challenging patient population is of great importance. Another limitation of this study is the relatively short follow-up period of 6 months to 24 months. Despite the retrospective study design, treatment and follow-up were according to protocol.

In conclusion, the results of our study show rapid and significant improvement in disease activity in children with intermediate and panuveitis treated with intravenous TCZ which was well tolerated. Future larger studies are needed to confirm the effectiveness and safety of intravenous TCZ in children with noninfectious uveitis. Our observation is therefore likely to be valuable for ophthalmologists and pediatric immunologists who treat children with uveitis.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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