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Short report

Tocilizumab effectiveness in paediatric non-infectious uveitis: data from the International AIDA Network Registries on ocular inflammatory disorders

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Received 19 February 2025
Accepted 23 April 2025
Published Online First
24 May 2025

ABSTRACT

To describe tocilizumab (TCZ) effectiveness in 15 children with refractory non-infectious uveitis. Reported outcomes are the number of relapses before and after treatment, steroid-sparing effect and drug retention rate. Macular oedema, fluorangiographic findings and ocular complications are also reported.

The mean number of ocular relapses significantly decreased from 314 per 100 eyes/year to 106 per 100 eyes/year ($p=0.016$). A significant steroid-sparing effect was detected ($p=0.037$). TCZ drug survival was 77.4% at 6 months, followed by 61.9% at 12, 24 and 36 months of follow-up. Macular oedema and retinal vasculitis resolved in all affected eyes.

INTRODUCTION

Paediatric non-infectious uveitis (NIU) represents a challenging condition to treat and may lead to irreversible visual loss in a considerable proportion of children.¹ Traditionally, glucocorticosteroids (GC) are used as a primary line of treatment. Nonetheless, it is essential to minimise chronic exposure to GC and reduce GC-related adverse events, especially in paediatric patients. Therefore, the treatment algorithm should consider the use of alternative treatments including conventional and biologic disease-modifying anti-rheumatic drugs. Despite the well-known efficacy of antitumour necrosis factor (anti-TNF) agents in the management of paediatric NIU,² treatment failures are encountered in roughly 30% of patients.³ This aspect highlights the need for alternative therapies that can effectively control intraocular inflammation and ensure sustained remission.

The evidence supporting the use of biological agents other than anti-TNF monoclonal antibodies, such as interleukin (IL) 6 inhibitors, in NIU remains limited. The role of IL-6 was demonstrated in experimental autoimmune models of NIU.⁴ Moreover, preliminary studies have disclosed promising results in the management of NIU with IL-6 inhibitors.^{5–7} In this context, we provide our multicentre experience regarding the effectiveness of Tocilizumab (TCZ) in paediatric NIU.

METHODS

Medical records of paediatric patients (onset before the age of 16) affected by NIU were reviewed. Data were extracted from the international AIDA Network for uveitis registry and Behçet's disease registries. Patients were treated with TCZ, either intravenously (8–12 mg/kg every 4 weeks) or subcutaneously (162 mg weekly).

The primary aim of the study was to assess the effectiveness of TCZ by measuring the number of relapses per 100 eyes per year before and after treatment. Secondary objectives included the evaluation of (a) the GC-sparing effect, (b) the TCZ drug retention rate (DRR) using Kaplan-Meier curves, (c) changes in visual acuity measured by the best corrected visual acuity (BCVA) expressed in decimals and (d) improvement in the number of eyes affected by macular oedema and retinal vasculitis. The record of new ocular complications during follow-up constituted the ancillary aim.

Data were analysed using SPSS (IBM Corp, Armonk, New York, USA). Normality was assessed with the Shapiro-Wilk test. Quantitative variables were reported as mean±SD or median (IQR), qualitative as frequencies (%). Group differences were tested with Student's t-test, Mann-Whitney U, or Wilcoxon tests, as required. Survival curves were estimated with the Kaplan-Meier method. Significance was set at $p<0.05$ (all tests were two-sided).

RESULTS

We enrolled 15 paediatric patients affected by NIU and treated with TCZ. Ocular involvement was bilateral in all of them except one. Figure 1 illustrates the steps leading to the final cohort of eligible patients. Table 1 details the demographic and clinical characteristics of the cohort.

We observed a significant relapse reduction from 314 to 106 per 100 eyes/year 12 months before and after TCZ ($p=0.016$) (figure 2A).

A GC-sparing effect was also observed ($p=0.037$). Mean GC dosage before and after TCZ initiation was 10.93 mg (median (IQR), 10 (21.88) mg) and 1.7 mg (median (IQR), 0 (0.50) mg), respectively. Regarding DRR, the estimated TCZ survival is



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To cite: Sota J, Breda L, Paroli MP, et al. *Br J Ophthalmol* 2025;**109**:1151–1154.

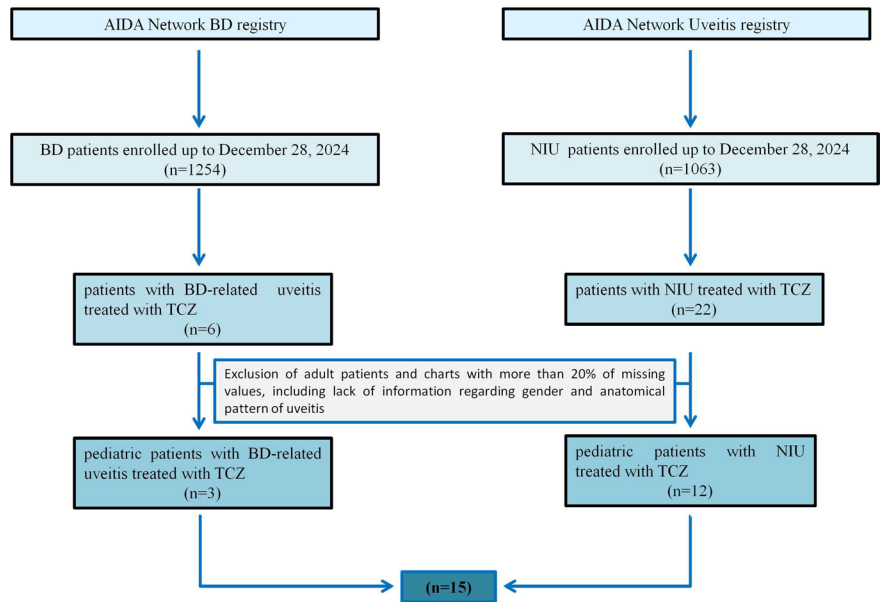


Figure 1 Flowchart showing the selection process for the paediatric patients included in the study. AIDA, Autoinflammatory Disease Alliance; BD, Behçet’s disease; NIU, non-infectious uveitis; TCZ, tocilizumab.

77.4% at 6 months, followed by a plateau after the 12th month of treatment (61.9% at 12, 24 and 36 months of follow-up) (figure 2B).

No differences were detected in median (IQR) BCVA between baseline values 0.95 (0.68) and the last follow-up assessment 1 (0.20) ($p=0.285$).

Children with juvenile idiopathic arthritis (JIA) had anterior uveitis in 11 eyes and intermediate uveitis in 2 eyes, while panuveitis was the dominant anatomical pattern (12), followed by posterior uveitis (2) and anterior uveitis (2) in the remaining cohort.

Macular oedema and retinal vasculitis were detected in four eyes at baseline and resolved in all of them by the last follow-up visit. No intravitreal drugs were used in conjunction with TCZ.

Ocular complications occurred in two eyes: one with macular atrophy and ischaemia, the other with retinal detachment, phthisis bulbi and band keratopathy.

DISCUSSION

The present study supports the effectiveness of IL-6 inhibition in paediatric NIU. Recent evidence highlights the pivotal role of IL-6 in NIU pathogenesis,⁸ providing the biological rationale for IL-6-targeted therapies. Indeed, IL-6 mediates inflammation in NIU and may also display a prognostic role, particularly in a specific subset of patients. More in detail, younger patients with associated systemic diseases and a high number of ocular flares tend to exhibit higher IL-6 serum levels, which could in turn

carry key therapeutic implications.⁹

The available medical literature is limited and, to some extent, controversial. In the APTITUDE trial, TCZ failed to meet the primary endpoint for treating TNF-refractory paediatric NIU associated with JIA,⁵ while showing encouraging results in a real-life setting.^{6,7}

Based on our findings, TCZ demonstrated an excellent response by significantly reducing the number of ocular relapses by almost threefold. Additionally, it showed remarkable drug survival, with an

Table 1 Demographic, clinical and therapeutic characteristics of our cohort

Patients (n)	15
Mean age at onset±SD (years)	6.18±2.84
Mean age at diagnosis±SD (years)	6.27±2.91
Mean diagnostic delay (months)—median (IQR)	1–0 (0.2)
Female/male	10/5
Ethnic origin	Caucasian (n=10)
	Arab (n=5)
Laterality	Bilateral (n=14)
	Monolateral (n=1)
Anatomical classification (eyes (n))	AU (n=13, 44.8%)
	IU (n=2, 6.9%)
	PU (n=2, 6.9%)
	PanU (n=12, 41.4%)
Associated systemic diseases	Juvenile idiopathic arthritis (n=7)
	Behçet’s disease (n=3)
	Mixed connective tissue disease (n=1)
	Idiopathic (n=4)
AU, anterior uveitis; IU, intermediate uveitis; PanU, panuveitis; PU, posterior uveitis.	

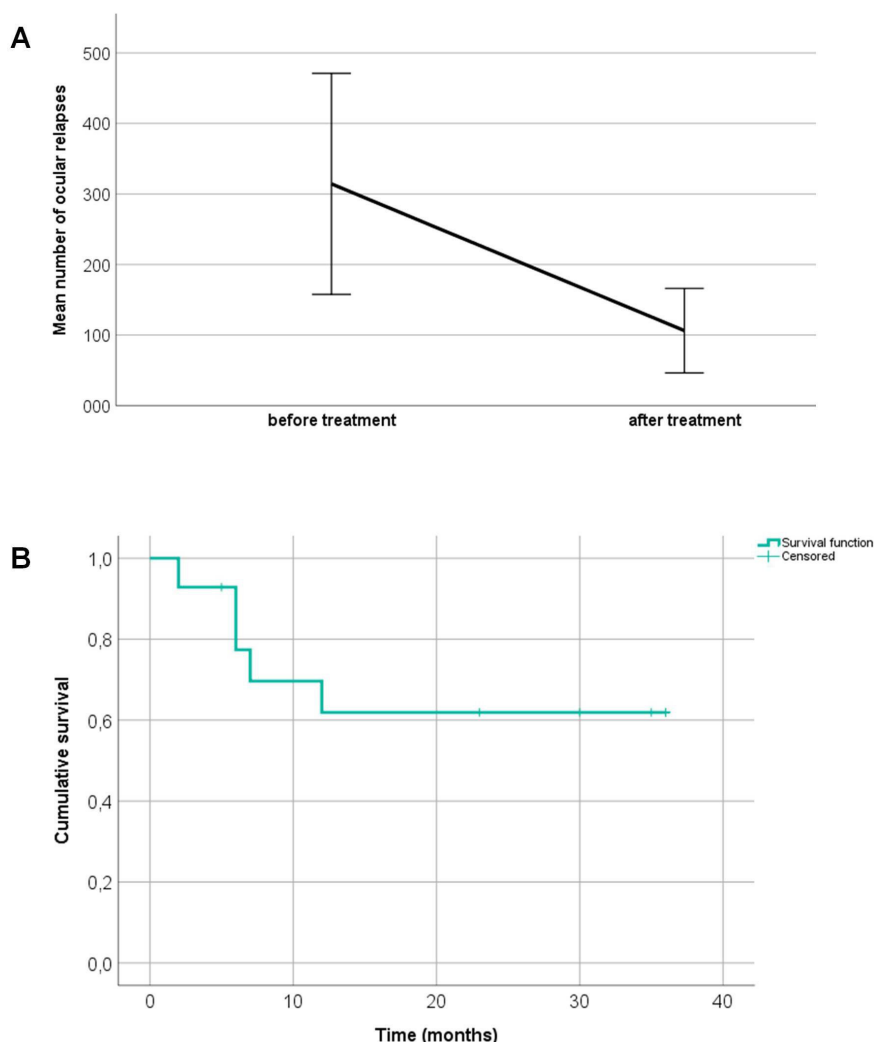


Figure 2 (A) Number of relapses per 100 eyes/year before and after treatment with tocilizumab (with 95% CI error bars). (B) Drug survival curve of tocilizumab (Kaplan-Meier method).

estimated probability of approximately 62% persistence after 3 years of treatment.

We also observed a significant steroid-sparing effect, which is especially important in paediatric-onset cases to reduce chronic GC exposure and its associated short- and long-term side effects, such as growth suppression. BCVA remained stable throughout the treatment period.

No eyes with retinal vasculitis or macular oedema were detected at the last follow-up. This suggests a potential role of IL-6 inhibition's efficacy in treating this complication.¹⁰ Finally, ocular complications occurred in only two eyes, likely due to early diagnosis (approximately 1-month delay).

Several substantial limitations should be mentioned. First, the small sample may limit generalisability. Second, variability in disease management across centres could introduce data heterogeneity, as different centres may follow different clinical practices and treatment protocols. Finally, the lack of randomisation may be responsible for a selection bias and potential confounders.

In summary, our findings support the effectiveness of TCZ in reducing relapses, sparing GC use and ensuring a favourable DRR in the treatment of paediatric NIU, while also preserving visual acuity. However, multicentre studies with larger sample sizes are needed to address unanswered questions in this emerging but largely unexplored field.

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Acknowledgements This research is supported (not financially) by the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA). AV, JS, BF, CF and LC belong to institutes that are members of the ERN RITA (Azienda Ospedaliero-Universitaria Senese of Siena). We

thank the University of Siena for the financial support in supporting the open access fees.

Contributors All the authors substantially contributed to the conception or design of the work and critically revised the paper. All the authors approved the final version and agreed to be responsible for all the aspects of the work. In addition, JS wrote the first draft of the manuscript and performed the preliminary data analysis and interpretation. JS, LB, MPP, SH, Ad-I-T, SG, AT, JC-L, MJAG, SLB, AV, EB, EDG, FM, SA-M, BF, LC and CF were involved in the study according to their active role in enrolling patients in the AIDA Network Registries for Uveitis and Behcet's Disease; CF, BF and LC took care of the final revision of the manuscript and accounted for the AIDA Registries Coordinator.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The Ethics Committee of Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. No. 14951; NCT05200715) approved the study, which was performed according to the Good Clinical Practice guidelines and the latest Declaration of Helsinki. Written informed consents for the involved patients were collected. Clinical data are kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and protecting privacy (2016/679/EU).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data underlying this article will be shared upon reasonable request to the corresponding author.

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