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REVIEW

Tocilizumab for Non-Infectious Uveitis: A Systematic Review

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Abstract: Non-infectious uveitis (NIU) comprises a heterogeneous group of diseases causing severe ocular inflammation that threatens vision. In addition to visual impairment, patients frequently endure chronic pain, functional disorders, and psychosocial stress, all of which substantially reduce quality of life. Treating NIU remains challenging because many patients respond inadequately to high-dose corticosteroids and various immunosuppressants. This systematic review evaluated the efficacy and safety of tocilizumab (TCZ) in NIU treatment by analyzing case reports and small-scale studies. A systematic search of PubMed, Web of Science, and Embase up to May 1, 2025, identified all published cases reporting baseline and follow-up visual acuity alongside intervention details. The Newcastle-Ottawa Scale (NOS) assessed methodological quality, while the Joanna Briggs Institute (JBI) tool evaluated risk of bias. The systematic review included 96 patients (36 males, 60 females) with an average age of 35 years (range 4–72). Behçet's disease (BD) represented the most common underlying condition (33 cases), and panuveitis was the primary anatomical subtype (35 cases). Prior to TCZ initiation, patients had received an average of 2.8 conventional immunosuppressants and 1.6 biologics, yet persistent disease activity remained. The median interval from diagnosis to TCZ treatment was 11.8 months (range 4–24). Following TCZ administration, vision improved in 62.5% of patients, intraocular inflammation was controlled in 83.3%, and macular edema resolved in 90.9%. Overall, 83.3% (80/96) responded favorably to TCZ. These findings indicate that TCZ may serve as an effective alternative for managing refractory NIU when other treatments fail.

Keywords: non-infectious uveitis, uveitis, tocilizumab, TCZ, interleukin-6, IL-6

Introduction

Non-infectious uveitis (NIU) is an immune-mediated disorder characterized by persistent visual impairment, including visual field defects, blurred vision, and ocular pain, and stands as a leading cause of preventable blindness worldwide.[1–3] NIU is classified into idiopathic cases without clear systemic associations and those related to systemic diseases. Juvenile idiopathic arthritis (JIA) represents the most common systemic cause of uveitis in children, with its associated uveitis (JIA-U) accounting for 20–30% of pediatric NIU cases, making it the second most prevalent subtype after idiopathic uveitis. Additional causes include sarcoidosis, Behçet's disease (BD), and Vogt-Koyanagi-Harada disease (VKH), among others.[4–6]

Current expert consensus recommends initiating NIU treatment with systemic or local corticosteroids.[4,7,8] However, prolonged corticosteroid use carries significant risks such as cataracts, glaucoma, and osteoporosis, restricting long-term application.[9–11] When inflammation remains uncontrolled by steroids, immunosuppressive agents like methotrexate and cyclosporine serve as second-line therapies.[12,13] Despite these options, many patients exhibit inadequate responses or intolerance to conventional immunomodulatory treatments, resulting in persistent refractory disease. In such cases, biologics targeting tumor necrosis factor-alpha (TNF-α), including adalimumab (ADA) and infliximab (IFX), become therapeutic choices for refractory NIU.[14–16]

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Nevertheless, the efficacy of TNF-α inhibitors remains suboptimal, with adverse events occurring relatively frequently.[17,18] IFX demonstrates lower tolerability due to a higher incidence of infusion-related reactions.[8,18] Both ADA and IFX achieve efficacy rates between 60% and 70% in NIU.[19–21] ADA's most commonly reported adverse effects include infections and injection-site reactions, affecting approximately 10–20% of patients, while IFX-related adverse events, such as infusion reactions and infections, occur at similar rates of 10–20%.[14,22–26] These limitations highlight the need to explore alternative therapies when conventional biologics fail.

Tocilizumab (TCZ), a recombinant humanized monoclonal antibody targeting the interleukin-6 receptor (IL-6R), exerts anti-inflammatory effects by inhibiting IL-6 binding.[27–29] Approved by the FDA for moderate-to-severe rheumatoid arthritis (RA), systemic JIA (s-JIA), and polyarticular JIA, TCZ also treats other inflammatory disorders such as giant cell arteritis (GCA), systemic sclerosis-associated interstitial lung disease (SSc-ILD), cytokine release syndrome (CRS), and severe COVID-19.[30–33]

Emerging evidence suggests that TCZ may offer a promising alternative for patients with NIU unresponsive to traditional immunosuppressants or biologics.[34–40] However, a comprehensive systematic review assessing its efficacy and safety remains lacking. This systematic review follows PRISMA 2020 guidelines to quantitatively synthesize published data, evaluate TCZ's therapeutic profile in NIU, and clarify its role and future prospects within existing treatment paradigms.

Methods

Search Strategy

The systematic review rigorously follows PRISMA 2020 guidelines and has been registered with PROSPERO under registration number CRD420251106755, ensuring transparency and methodological rigor. A comprehensive search of PubMed, Web of Science, and Embase was performed to identify case reports and case series on TCZ use in NIU published up to May 1, 2025, without language restrictions. The search strategy combined subject headings and free-text terms using Boolean operators. For example, the PubMed query included: ((“Uveitis”[Mesh] OR Uveitis OR “non-infectious uveitis”) AND ((“Interleukin-6” OR “Interleukin 6” OR IL-6 OR “B Cell Stimulatory Factor-2” OR BSF-2 OR “Hepatocyte-Stimulating Factor” OR “Interferon beta-2” OR IL6) OR (TCZ OR tocilizumab OR “monoclonal antibody, MRA” OR atlizumab OR Actemra OR Roactemra OR RHPM-1 OR RG-1569 OR RO-4877533 OR R-1569 OR MSB11456 OR MSB-11456 OR BAT-1806 OR BAT1806))) AND (“1900/01/01”[Date - Entry]: “2025/05/01”[Date - Entry])). Additionally, reference lists from pertinent articles underwent manual screening to identify further eligible studies. Initial literature screening and data extraction were conducted by H.C. and K.B, with subsequent review and verification by X.M. to ensure accuracy and methodological integrity. The study selection process is detailed in Figure 1.

Inclusion Criteria

Inclusion criteria were as follows: (1) patients with a confirmed NIU diagnosis according to the Standardization of Uveitis Nomenclature (SUN) criteria, encompassing anterior, intermediate, posterior, or panuveitis;[41] (2) treatment with TCZ via any administration route (intravenous or subcutaneous) at any dose; (3) case reports or series providing comprehensive patient-level data, including baseline demographics, etiology, anatomical classification, best-corrected visual acuity (BCVA) before and after treatment, inflammatory activity, central foveal thickness (CFT) changes, and prior immunosuppressive or biologic therapy; (4) Newcastle-Ottawa Scale (NOS) scores ≥4, reflecting moderate to high methodological quality. H.C. and K.B. performed the initial assessment, followed by X.M.'s review and validation to ensure completeness and accuracy.

Exclusion Criteria

Exclusion criteria were as follows: (1) duplicate publications, articles lacking original data, conference abstracts, reviews, animal studies, and studies with NOS scores below 4, indicating low quality; (2) studies reporting only aggregate data without extractable patient-level efficacy or safety outcomes; (3) studies including individuals younger than 2 years or older than 80 years without separate data for pediatric or geriatric subgroups; (4) studies failing to clearly report TCZ

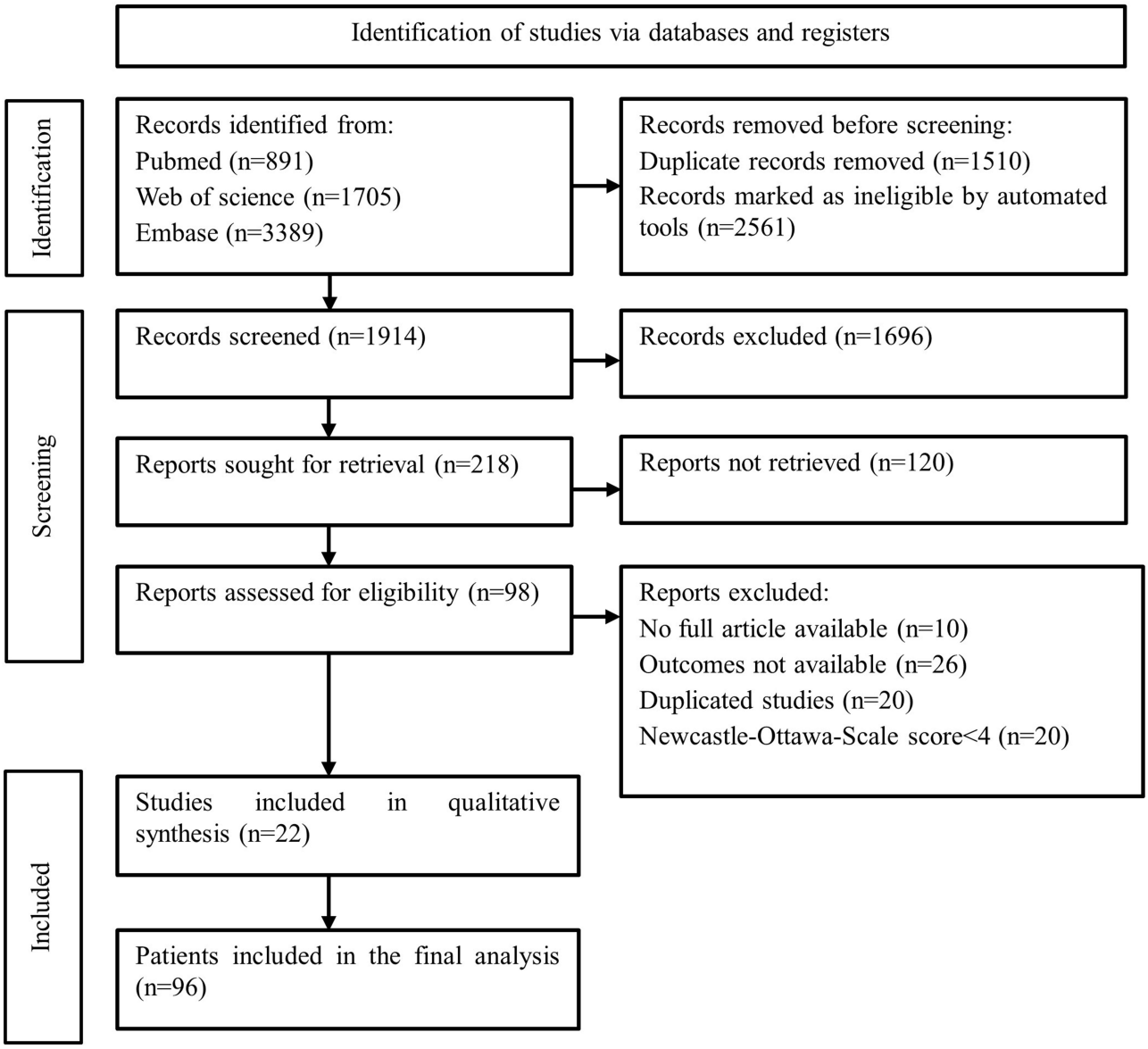

Figure 1 PRISMA flowchart for the systematic review.

dosage, administration intervals, or treatment duration, or mixing multiple dosing regimens without stratified analyses; (5) studies primarily assessing inflammation outside the eyes (eg, joints, skin, intestines) where NIU-specific data could not be isolated; and (6) studies focusing predominantly on pharmacoeconomics, cost-effectiveness, quality of life measures, or patient-reported outcomes (PROs) without objective clinical indicators.

Data Collection

A standardized data extraction form captured patient characteristics and efficacy and safety outcomes. Extracted variables included age, sex, anatomical uveitis classification, laterality (unilateral or bilateral), baseline and follow-up BCVA, ocular complications, prior immunosuppressant and biologic use, and interval from symptom onset to TCZ initiation (in weeks). Details of the TCZ regimen—dosage and frequency—and treatment-emergent adverse events were documented. Imaging data included changes in CFT measured by optical coherence tomography (OCT) before and after TCZ therapy. Macular edema was defined as baseline CFT > 350 μm, with resolution marked by post-treatment CFT < 300 μm. Visual

acuity changes were classified as "improved" if follow-up BCVA exceeded baseline or "deteriorated" if worse. This comprehensive dataset enabled thorough assessment of TCZ's clinical efficacy and safety in NIU.[42]

Quality Assessment and Risk of Bias

The Joanna Briggs Institute (JBI) critical appraisal tools were applied according to study type—case reports, cohort studies, and case series—to evaluate risk of bias. N.Z. and C.M. independently completed assessments for each article and answered all JBI checklist items. Discrepancies were resolved through consultation, followed by review and verification by X.M. Studies with only one "No" response on the JBI checklist were classified as having low risk of bias. After the evaluation by JBI, we considered all the literature as "low risk of bias".

Response Criteria

Efficacy was evaluated using a composite endpoint widely adopted in international uveitis research.[41,42] TCZ treatment qualified as effective if any of the following criteria were met: (a) a reduction of at least two grades in anterior chamber or vitreous inflammatory cell count from baseline, or reduction to grade 0, based on SUN criteria; (b) a decrease in systemic prednisone dosage to ≤10 mg/day (or equivalent corticosteroid) while maintaining uveitis control; (c) resolution of macular edema, defined as OCT-measured CFT <300 μm, with sustained uveitis control; or (d) overall clinical improvement as assessed by the original study authors. The primary outcome focused on reducing ocular inflammation, while relapse was defined as recurrence of active inflammation after remission.

Statistical Analysis

All extracted data underwent analysis using SPSS version 26.0. Categorical variables were summarized as frequencies and percentages, whereas continuous variables were expressed as mean ± standard deviation or median (range), contingent on data distribution. Chi-square tests examined associations between categorical variables—such as etiology, uveitis type, and TCZ regimen—and treatment response (effective vs ineffective). This test evaluates whether observed frequencies significantly deviate from expected values across categories, applying a significance threshold of $p < 0.05$.

Logistic regression analysis assessed the influence of categorical predictors on the likelihood of treatment success. Independent variables included etiology, uveitis type, and TCZ regimen, with treatment response as the binary dependent variable. Model fit was evaluated using McFadden's R^2, and odds ratios (OR) with 95% confidence intervals (CI) quantified the strength of associations.

Results

Baseline Characteristics of TCZ-Treated Patients

The literature search identified 5985 potentially relevant articles. Applying inclusion and exclusion criteria narrowed this to 22 studies (case reports or case series) included in the analysis. Due to incomplete individual-level data in some reports, detailed clinical information from 96 patients was extracted for this systematic review, summarized in Table 1. The patients' mean age was approximately 35 years (range 4–72), with 62.5% (60/96) female. According to the SUN classification, panuveitis represented the most prevalent subtype (35%, 34/96), followed by anterior uveitis (17%, 16/96), intermediate uveitis (7%, 7/96), and posterior uveitis (4%, 4/96). Some studies did not specify anatomical classification. The most common underlying diseases included JIA, BD, and RA, as detailed in Table 2.

Prior Treatments Before TCZ Initiation

Before TCZ initiation, patients had undergone multiple treatments. Intravitreal corticosteroid injections were administered to 72.9% (70/96) of patients (Table 1). Systemic conventional immunosuppressants were widely used: methotrexate in 65.6% (63/96) and cyclosporine A in 50% (48/96). Biologic therapies were also frequent, with ADA used in 76% (73/96). TCZ was introduced after high-dose corticosteroids, conventional immunosuppressants, or other biologics failed to control progressive intraocular inflammation adequately.

Table 1 Baseline Characteristics and Prior Therapies of Patients with NIU

Patient Number	96
Age at TCZ initiation (mean, range; years)	35 (4–72 years)
Sex (Female/Male)	60/36
Immunosuppressants prior to TCZ (n)	
AZA	31
MMF	35
MTX	63
LEF	1
CYA	48
PRED	70
CFM	2
IFN-a	14
Biological prior to TCZ (n)	
ADA	73
ETA	7
GLM	3
IFX	64
RTX	3
ABA	4
Ocular complications prior to TCZ (n)	
ICE	6
Glaucoma	4
CAT	14
CME	46
VE	2
RA	21
PPE	1
BDK	1
RC	6
LN	1
AS	1
KP	1
RD	1

Abbreviations: AZA, Azathioprine; MMF, Mycophenolate Mofetil; MTX, Methotrexate; LEF: Leflunomide; CYA, Cyclosporine A; PRED, Prednisone; CFM, Cyclophosphamide; ADA, Adalimumab; ETA, Etanercept; GLM, Golimumab; IFX, Infliximab; RTX, Rituximab; ABA, Abatacept; ICE, Iridocorneal Endothelial Syndrome; Glaucoma, Glaucoma; CAT, Cataract; CME, Cystoid Macular Edema; VE, Vitritis; RA, Retinal Vasculitis; PPE, Papilledema; BDK, Band Keratopathy; RC, Retinochoroiditis; LN, Lupus Nephritis; AS, Anterior Synechia; KP, Keratic Precipitates; RD, Retinal Detachmen.

Statistical Analysis Results

Chi-square tests revealed no significant associations between etiology, uveitis type, or TCZ regimen and treatment response ($p > 0.05$), as summarized in Table 3.

Logistic regression analysis (Table 4) confirmed that none of these variables significantly influenced the likelihood of a favorable response to TCZ (all $p > 0.05$). The McFadden R^2 of 0.134 indicates that these factors explain only a modest proportion of variability in treatment outcomes.

Table 2 The Clinical Course of NIU Patients Receiving TCZ Treatment

Ref	Patient (Age/ Sex)	Etiology	Uveitis Type	VA Before TCZ (L / R, μm)	VA Before TCZ (L / R, μm)	CFT Before TCZ (L / R, μm)	CFT After TCZ (L / R, μm)	TCZ Regimen	NOS Score	Follow-Up Time	TCZ Response
1[11]	1/69/F	BSCR	Posterior	20/50 20/50	20/25 20/32	372 452	218 372	8mg/kg IVq4w	5	6m	Effective
	2/27/F	Au	Panuveitis	20/30 20/30	20/20-	-288	-258	8mg/kg IVq4w			Effective
2[43]	3/58/M	MCD	-	0.4 0.7	0.5 0.9	–	–	8mg/kg IVq4w	4	3m	Effective
3[44]	4/69/M	Cogan(aortitis)	-	Finger50cm 0.7	Stable	–	–	8mg/kg IVq4w	4	7m	Effective
4[45]	5/18/M	JIA	Anterior	–	–	–	–	-	4	9m	Ineffective
	6/18/F	PA	Anterior	–	–	–	–	-			Effective
	7/19/F	PA	Anterior	–	–	–	–	-			Effective
5[46]	8/29/F	JIA	Panuveitis	0.2 Finger50cm	-20/80	775 775	264 264	8mg/kg IVq4w	5	12m	Effective

6[47]	9/30/F	JIA	-	0.8 0.8	0.5 0.5	424 424	197 197	8mg/kg IVq4w	6	6m	Effective
	10/56/F	IPU	-	1.3 1.3	1.0 1.0	896 896	176 176	8mg/kg IVq4w			Effective
	11/54/F	BSCR	-	0.4 0.4	0.2 0.2	500 500	345 345	8mg/kg IVq4w			Effective
	12/54/F	BSCR	-	0.3 0.3	0.2 0.2	260 260	246 246	8mg/kg IVq4w			Effective
	13/68/F	BSCR	-	0.3 0.3	0.4 0.4	590 590	320 320	8mg/kg IVq4w			Effective
	14/68/F	BSCR	-	0.4 0.4	0.3 0.3	528 528	471 471	8mg/kg IVq4w			Effective
	15/39/F	BSCR	-	0.7 0.7	0.2 0.2	974 974	267 267	8mg/kg IVq4w			Effective
	16/39/F	BSCR	-	0.4 0.4	0.1 0.1	644 644	334 334	8mg/kg IVq4w			Effective
7[30]	17/72/F	RA	-	–	–	–	–	8mg/kg IVq4w	6	-	Ineffective
8[48]	18/12/M	JIA	Anterior	–	–	–	–	8mg/kg IVq4w	4	-	Effective

(*Continued*)

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Table 2 (Continued).

Ref	Patient (Age/ Sex)	Etiology	Uveitis Type	VA Before TCZ (L / R, μm)	VA Before TCZ (L / R, μm)	CFT Before TCZ (L / R, μm)	CFT After TCZ (L / R, μm)	TCZ Regimen	NOS Score	Follow-Up Time	TCZ Response
9[42]	19/31/F	JIA	Panuveitis	0.8 0.8	0.5 0.5	424 424	221 221	8mg/kg IVq4w	7	12m	Effective
	20/60/F	BSCR	Panuveitis	0.4 0.4	0.3 0.2	260 500	230 254	8mg/kg IVq4w			Effective
	21/70/F	BSCR	Panuveitis	0.3 0.3	0.3 0.3	528 590	307 351	8mg/kg IVq4w			Effective
	22/40/F	BSCR	Panuveitis	0.7 0.4	0.1 0.2	644 974	321 346	8mg/kg IVq4w			Effective
	23/23/F	JIA	Panuveitis	0.8 0.8	0.6 0.6	577 577	278 278	8mg/kg IVq4w			Effective
	24/24/F	JIA	Panuveitis	0.1 0.1	–	334 321	267 272	8mg/kg IVq4w			Effective
10[49]	25/37/F	RA	-	0.8 0.8	1 1	–	–	8mg/kg IVq4w	8	7.3±5.7m	Effective
	26/42/F	BD	-	0.6 0.4	0.5 0.8	–	–	8mg/kg IVq4w			Ineffective
	27/67/F	BD	-	0.01 0.01	0.01 0.01	–	–	8mg/kg IVq4w			Effective

11[50]	28/71/F	BSCR	Panuveitis	0.4 0.15	0.045 0	–	–	8mg/kg IVq4w	6	-	Effective
	29/40/M	IPU	Panuveitis	–	–	–	–	8mg/kg IVq4w			Effective
	30/28/F	IPU	Panuveitis	0.22 0	0.1 0.1	–	–	8mg/kg IVq4w			Effective
	31/42/F	IPU	Panuveitis	1.0 2.0	1 1	–	–	8mg/kg IVq4w			Ineffective
	32/47/M	IPU	Panuveitis	0.22 1.3	0.1 0.6	–	–	8mg/kg IVq4w			Effective
	33/40/M	BD	Panuveitis	1.0 2.0	1.0 2.0	–	–	8mg/kg IVq4w			Ineffective
	34/48/F	IPU	Panuveitis	0.7 2.0	0.7 2.0	–	–	8mg/kg IVq4w			Effective
	35/21/M	IPU	Panuveitis	0.1 0.22	0.1 0.15	–	–	8mg/kg IVq4w			Effective
12[48]	36/12/M	JIA	Panuveitis	20/50 20/40	–	–	–	-	6	-	Effective
13[45]	37/18/M	JIA	Anterior	–	–	–	–	8mg/kg IVq4w	6	-	Effective
	38/18/F	JIA	Anterior	–	–	–	–	8mg/kg IVq4w			Ineffective
	39/19/F	JIA	Anterior	–	–	–	–	9mg/kg			Effective

(*Continued*)

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Table 2 (Continued).

Ref	Patient (Age/ Sex)	Etiology	Uveitis Type	VA Before TCZ (L / R, μm)	VA Before TCZ (L / R, μm)	CFT Before TCZ (L / R, μm)	CFT After TCZ (L / R, μm)	TCZ Regimen	NOS Score	Follow-Up Time	TCZ Response
14[51]	40/14/F	JIA	Anterior	–	–	–	–	8mg/kg IVq4w	6	18-35m	Effective
	41/26/F	JIA	Panuveitis	–	–	–	–	4mg/kg			Effective
	42/58/F	BD	-	–	–	–	–	4/8mg/kg IVq4w			Effective
	43/36/M	IPU	Panuveitis	–	–	–	–	4/8mg/kg IVq4w			Effective
	44/45/F	IPU	Intermediate uveitis	–	–	–	–	8mg/kg IVq4w			Effective
	45/25/F	JIA	Anterior	–	–	–	–	4/8mg/kg IVq4w			Ineffective
	46/50/F	JIA	Panuveitis	–	–	–	–	4/8mg/kg IVq4w			Ineffective
	47/24/F	JIA	Panuveitis	–	–	–	–	4mg/kg			Effective
	48/30/F	IPU	Anterior	–	–	–	–	8mg/kg IVq4w			Ineffective
	49/33/F	JIA	Anterior	–	–	–	–	4/8mg/kg IVq4w			Effective
15[52]	50/24/F	JIA	Anterior	0.3 1.3	0.1 0.8	750 210	530 190	-	6	-	Effective
	51/23/F	JIA	Anterior	0.8 0.8	0.7 0.7	640 150	–	-			Effective
	52/57/F	RA	Intermediate uveitis	0.4 0.1	0.7 0.3	640 530	540 300	-			Effective
	53/53/M	RA	Anterior	1.0 1.7	1.4 1.0	960 820	660 630	-			Effective
	54/56/M	AS	Anterior	0.3 0.3	–	700 200	–	-			Effective

16[53]	55/27/M	BD	Posterior	–	–	–	–	-	6	9.5m	Ineffective
	56/42/F	BD	Panuveitis	–	–	–	–	-			Ineffective
	57/50/M	BD	Panuveitis	–	–	–	–	-			Effective
	58/35/M	BD	Panuveitis	–	–	–	–	-			Effective
	59/67/F	BD	Panuveitis	–	–	–	–	-			Effective
	60/31/M	BD	Panuveitis	–	–	–	–	-			Effective
	61/22/F	BD	Panuveitis	–	–	–	–	-			Effective
	62/75/M	BD	Panuveitis	–	–	–	–	-			Effective
	63/10/M	BD	Panuveitis	–	–	–	–	-			Effective
	64/48/F	BD	Panuveitis	–	–	–	–	-			Effective
	65/16/M	BD	Panuveitis	–	–	–	–	-			Effective
	66/40/M	IPU	Panuveitis	–	–	–	–	-			Effective
17[54]	67/35/F	BSCR	Posterior	–	20/20 20/160	467 690	-279	-	5	-	Effective
	68/39/F	BSCR	Posterior	20/25 20/32	20/25 20/25	372 283	252 250	-			Effective
18[55]	69/13/M	IPU	Anterior	6/24 6/9	6/9 6/6	–	–	-	4	13m	Effective
19[56]	70/33/F	MS	Panuveitis	0.4logMAR 1.3logMAR	0.1logMAR 0.1logMAR	-720	-168	-	4	3m	Effective
20[57]	71/26/F	JIA	-	20/80 20/20	20/40 20/20	–	–	-	4	8m	Effective

(*Continued*)

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Table 2 (Continued).

Ref	Patient (Age/ Sex)	Etiology	Uveitis Type	VA Before TCZ (L / R, μm)	VA Before TCZ (L / R, μm)	CFT Before TCZ (L / R, μm)	CFT After TCZ (L / R, μm)	TCZ Regimen	NOS Score	Follow-Up Time	TCZ Response
21[58]	72/5/M	RIU	Intermediate uveitis	–	–	–	–	-	6	6-24m	Ineffective
	73/4/F	RIU	Intermediate uveitis	–	–	–	–	-			Ineffective
	74/3/M	RIU	Intermediate uveitis	–	–	–	–	-			Effective
	75/9/M	RIU	Intermediate uveitis	–	–	–	–	-			Effective
	76/11/M	RIU	-	–	–	–	–	-			Effective
	77/7/F	RIU	Panuveitis	–	–	–	–	-			Effective
	78/6/F	RIU	Panuveitis	–	–	–	–	-			Effective

22[59]	79/33/F	BD	-	–	–	–	–	-	6	-	Effective
	80/16/F	BD	-	–	–	–	–	-			Effective
	81/29/F	BD	-	–	–	–	–	-			Effective
	82/65/F	BD	-	–	–	–	–	-			Effective
	83/24/F	BD	-	–	–	–	–	-			Effective
	84/21/M	BD	-	–	–	–	–	-			Effective
	85/26/F	BD	-	–	–	–	–	-			Effective
	86/9/M	BD	-	–	–	–	–	-			Effective
	87/27/M	BD	-	–	–	–	–	-			Effective
	88/24/M	BD	-	–	–	–	–	-			Effective
	89/29/M	BD	-	–	–	–	–	-			Ineffective
	90/32/F	BD	-	–	–	–	–	-			Effective
	91/31/M	BD	-	–	–	–	–	-			Effective
	92/32/M	BD	-	–	–	–	–	-			Effective
	93/29/M	BD	-	–	–	–	–	-			Ineffective
	94/22/M	BD	-	–	–	–	–	-			Ineffective
	95/48/F	BD	-	–	–	–	–	-			Effective
	96/32/M	BD	-	–	–	–	–	-			Effective

Abbreviations: AU, Autoimmune Uveitis; MCD, Multicentric Castelmann Disease; PA, Polyarthritis; Cogan, Cogan syndrome complicated with aortitis; BSCR, Birdshot Choroidoretinopathy; BD, Behcet's Disease; IPU, Idiopathic Uveitis; RIU, Refractory Idiopathic Uveitis; MS, Multiple Sclerosis; AS, Ankylosing Spondyliti; CFT, Central Foveal Thickness; VA, Visual Acuity; RA, Rheumatoid Arthritis. NOS, Newcastle-Ottawa Scale.

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Table 3 Chi-Square Test Results

Variable	Name	TCZ Response(%)		Total(n)	χ2	p
		Effective	Ineffective			
Etiology	AS	1(100.000)	0(0.000)	1	5.565	0.901
	Au	1(100.000)	0(0.000)	1		
	BD	26(78.788)	7(21.212)	33		
	BSCR	13(100.000)	0(0.000)	13		
	Cogan(aortitis)	1(100.000)	0(0.000)	1		
	IPU	10(83.333)	2(16.667)	12		
	JIA	16(80.000)	4(20.000)	20		
	MCD	1(100.000)	0(0.000)	1		
	MS	1(100.000)	0(0.000)	1		
	PA	2(100.000)	0(0.000)	2		
	RA	3(75.000)	1(25.000)	4		
	RIU	5(71.429)	2(28.571)	7		
Uveitis Type	Anterior	12(75.000)	4(25.000)	16	2.640	0.451
	Intermediate uveitis	4(66.667)	2(33.333)	6		
	Panuveitis	31(88.571)	4(11.429)	35		
	Posterior	3(75.000)	1(25.000)	4		
TCZ Regimen	4/8mg/kg IVq4w	3(60.000)	2(40.000)	5	2.400	0.494
	4mg/kg	2(100.000)	0(0.000)	2		
	8mg/kg IVq4w	31(83.784)	6(16.216)	37		
	9mg/kg	1(100.000)	0(0.000)	1		

Abbreviations: AS, Ankylosing Spondylitis; AU, Autoimmune Uveitis; BD, Behçet's Disease; BSCR, Birdshot Chorioretinopathy; Cogan, Cogan Syndrome with aortitis; IPU, Idiopathic Uveitis; JIA, Juvenile Idiopathic Arthritis; MCD, Multicentric Castleman Disease; MS, Multiple Sclerosis; PA, Polyarthritis; RA, Rheumatoid Arthritis; RIU, Refractory Idiopathic Uveitis.

Table 4 Logistic Regression Analysis Results

Variable	Coefficient	Standard Error	z-Value	Wald χ2	p-value	OR	OR 95% CI
Etiology	0.378	0.420	0.901	0.812	0.368	1.460	0.641 ~ 3.323
Uveitis Type	0.890	0.611	1.457	2.123	0.145	2.436	0.735 ~ 8.070
TCZ Regimen	0.845	0.623	1.356	1.840	0.175	2.328	0.686 ~ 7.898
Intercept	−5.106	4.245	−1.203	1.446	0.229	0.006	0.000 ~ 24.901

Notes: Dependent Variable = TCZ Response; McFadden R^2 = 0.134.

TCZ Efficacy and Macular Edema Response

TCZ demonstrated a high overall efficacy rate of 83.3% (80/96), as shown in Table 2. Subgroup analysis by etiology revealed the following response rates: Birdshot chorioretinopathy (BSCR), 19 cases (19.8%, 19/96), with all patients achieving clinical efficacy (100%, 19/19); JIA-associated uveitis, 14 cases (14.6%, 14/96), with 10 patients responding to treatment (71.4%, 10/14); BD-associated uveitis, 33 cases (34.3%, 33/96), with 26 effective responses (78.8%, 26/33); RA-associated uveitis, 4 cases (4.2%, 4/96), with 3 patients responding (75%, 3/4); idiopathic panuveitis (IPU), 12 cases (12.5%, 12/96), with 10 effective responses (83.3%, 10/12); refractory idiopathic uveitis (RIU), 7 cases (7.3%, 7/96), with 5 patients responding (71.4%, 5/7); multicentric Castleman disease (MCD), 1 case (1%, 1/96), with efficacy observed in the single case (100%, 1/1); Cogan syndrome with aortitis, 1 case (1%, 1/96), with complete response (100%, 1/1); multiple sclerosis (MS), 1 case (1%, 1/96), with full efficacy (100%, 1/1); psoriatic arthritis (PA), 2 cases (2%, 2/96), both achieving response (100%, 2/2); autoimmune uveitis (AU), 1 case (1%, 1/96), effective (100%, 1/1); and ankylosing spondylitis (AS), 1 case (1%, 1/96), also effective (100%, 1/1). Among all patients, 83.3% (80/96) met clinical efficacy criteria, characterized by significant reduction in intraocular inflammation along with either stabilized or improved visual acuity. Specifically, visual acuity improved in 60 patients (62.5%), remained stable in 6 (6.3%), and declined in 20 (20.8%) following treatment. In the subset of 22 patients with quantifiable macular edema evaluated by OCT, TCZ achieved a resolution rate of 90.9% (20/22), evidenced by normalization of CFT. Only 2 patients (9.1%) exhibited persistent refractory macular edema, indicating high efficacy of TCZ in macular edema management within this cohort.

TCZ Failures, Adverse Events, and Etiology-Specific Outcomes

Although most patients responded favorably to TCZ, 16 cases (16.7%, 16/96) were classified as treatment failures (Table 5). A systematic literature review identified common characteristics among these non-responders: (a) initiation of TCZ during late-stage disease with irreversible ocular damage—such as retinal detachment or refractory macular fibrosis—where inflammation control failed to restore function; (b) treatment discontinuation due to severe adverse events, including infusion-related reactions, serious infections, or laboratory abnormalities like marked neutropenia, which compromised sustained inflammation control; (c) development of severe ocular complications during TCZ therapy, such as cataract progression or retinal detachment, negatively impacting efficacy evaluation; and (d) suboptimal treatment regimens involving inadequate dosing or premature discontinuation, indicating insufficient treatment intensity or exposure contributed to failure.

Most patients exhibited improvement in inflammatory markers alongside successful corticosteroid tapering. Mean visual acuity also improved post-treatment. Adverse events of varying severity occurred in approximately 34 patients (35%) (Table 5), with the most common being infusion reactions, elevated liver enzymes, and increased infection risk. The majority of adverse events proved manageable through monitoring and appropriate interventions. Nevertheless, a few patients discontinued TCZ due to serious adverse events, including one case of a severe anaphylactic infusion reaction.

Discussion

This systematic review of current literature demonstrates that TCZ achieves a high clinical remission rate in NIU, with an efficacy of 83.3% (80/96), significantly improving both inflammation control and visual function.[2,60,61] These findings align with recent studies; for example, Uludag et al observed seven cases of refractory uveitis and reported that intravenous TCZ administration led to a substantial reduction in central retinal thickness and improved fluorescein angiography scores, accompanied by minimal severe adverse events, thus supporting TCZ's efficacy and safety.[62] Similarly, a multicenter study involving 11 patients with BD-associated uveitis documented rapid improvement in all ocular inflammation markers following TCZ initiation, with eight patients achieving complete remission.[59] These independent studies further validate the high remission rate observed in this systematic review. However, the response to TCZ treatment may vary among different patient populations. In the Phase II APTITUDE trial for JIA-associated uveitis, the primary endpoint response rate was approximately 34%, falling short of expectations.[63] Nonetheless, the trial

Table 5 Adverse Reactions During TCZ Therapy

Patient (Age/Sex)	Adverse Reaction(s)
17/72/F	Severe malaise and dizziness
18/12/M	Neutropenia
28/71/F	Bronchitis
29/40/M	Leukopenia and thrombocytopenia
36/12/M	Neutropenia
45/25/F	Neutropenia; intolerable dizziness and nausea; severe angioedema; severe abdominal pain
46/50/F	Neutropenia; intolerable dizziness and nausea; severe angioedema; severe abdominal pain
48/30/F	Neutropenia; intolerable dizziness and nausea; severe angioedema; severe abdominal pain
55/27/M	Severe infusion reaction; oral ulcers; asymptomatic cerebral white matter lesion; arthritis; folliculitis
56/42/F	Oral and genital ulcers; erythema nodosum; arthritis
57/50/M	Papillitis (optic neuritis); arthritis
58/35/M	Oral ulcers; folliculitis
59/67/F	Livedo reticularis (reticular purpura)
60/31/M	Oral and genital ulcers; folliculitis
62/75/M	Oral and genital ulcers; arthritis; folliculitis
63/10/M	Oral and genital ulcers; hemorrhagic stroke; erythema nodosum
64/48/F	Oral and genital ulcers; arthritis; pseudofolliculitis; erythema nodosum
67/39/F	Pulmonary infection (no hospitalization needed)
72/5/M	Neutropenia and multiple cervical lymphadenopathy
79/33/F	Oral and genital ulcers; erythema nodosum; arthralgia
80/16/F	Pseudofolliculitis; erythema nodosum; arthralgia
81/29/F	Oral ulcers; carotid aneurysm
82/65/F	Oral ulcers; arthralgia
83/24/F	Oral ulcers; arthralgia
84/21/M	Oral ulcers; pyoderma gangrenosum
85/26/F	Oral and genital ulcers; pseudofolliculitis; hidradenitis suppurativa; arthralgia
86/9/M	Oral ulcers
97/27/M	Arthralgia
88/24/M	Oral and genital ulcers; arthralgia
89/29/M	Refractory retinal vasculitis; oral ulcers; pseudofolliculitis; arthralgia
90/32/F	Oral and genital ulcers; pseudofolliculitis; arthralgia; venous thrombosis; pericarditis
91/31/M	Oral ulcers
92/32/M	Oral ulcers; pseudofolliculitis; arthralgia

(*Continued*)

Table 5 (Continued).

Patient (Age/Sex)	Adverse Reaction(s)
93/29/M	Refractory retinal vasculitis; oral ulcers; pseudofolliculitis; arthralgia
94/22/M	Oral ulcers; papulopustular lesions; erythema nodosum
95/48/F	Oral and genital ulcers; pseudofolliculitis; arthralgia
96/32/M	Oral ulcers; pseudofolliculitis; arthralgia

highlighted that some patients unresponsive to conventional immunosuppressants and anti-TNF therapies experienced inflammation control after switching to TCZ.[6,25] Currently, no direct comparative studies exist between TNF inhibitors and TCZ in the context of NIU, and a large proportion of patients transition to TCZ after failure of corticosteroids or TNF inhibitors. Therefore, direct comparisons of efficacy between TCZ and corticosteroids or TNF inhibitors are not yet possible. Overall, these findings reinforce TCZ's role as a valuable rescue therapy in NIU and emphasize the necessity for further research to better define its efficacy within specific patient subgroups.

Mechanistically, IL-6 involvement in uveitis pathogenesis offers a compelling rationale for TCZ's effectiveness.[6] NIU is characterized by an imbalance between pro-inflammatory Th17 cells and anti-inflammatory regulatory T (Treg) cells.[64–66] IL-6 serves as a pivotal cytokine driving differentiation of naïve CD4+ T cells into the Th17 lineage, particularly in the presence of transforming growth factor-β.[2,67,68] Numerous studies confirm hyperactivation of IL-6-mediated signaling in autoimmune ocular inflammation, closely correlating with disease activity.[69–72] Experimental uveitis models demonstrate that IL-6 knockout or anti-IL-6 monoclonal antibody treatment significantly suppresses retinal inflammation.[73–77] By blocking IL-6R interaction, TCZ disrupts the inflammatory feedback loop and mitigates immune-mediated ocular damage, forming the basis of its mechanism of action.[73] As an IL-6R antagonist, TCZ binds both soluble and membrane-bound IL-6R, inhibiting downstream IL-6/IL-6R/gp130 complex signaling, thereby reducing pro-inflammatory cytokine production and recruitment of inflammatory cells, including neutrophils.[78] Some reports suggest that TCZ not only suppresses pathogenic Th17 responses but also helps restore the Th1/Th17 balance, enhancing immune regulation within the retinal microenvironment—an effect critical for controlling refractory ocular inflammation.[71,73,79] Collectively, these findings underscore TCZ's considerable therapeutic potential for managing NIU.

A key finding of this study is that early initiation of TCZ may enhance therapeutic outcomes.[80] Patients receiving TCZ early in the disease course generally experienced better recovery, whereas delayed treatment proved less effective at reversing irreversible visual loss. This suggests that for NIU refractory to conventional therapies, introducing biologics with novel mechanisms early—rather than repeatedly using agents within the same class—may better prevent cumulative tissue damage.[42] This approach is especially critical for severe, vision-threatening cases, such as refractory Behçet's uveitis, where early TCZ intervention may reduce the risk of recurrent retinal injury from relapses. However, the precise definition of "early" treatment remains ambiguous; it likely refers to initiation within months of NIU diagnosis and treatment failure, rather than years later when irreversible ocular damage has occurred. Clinical practice should emphasize personalized TCZ strategies, including decisions on combination with conventional immunosuppressants, administration route (intravenous versus subcutaneous), and dosage adjustments.[27,81] Comparative studies indicate some refractory cases respond better to intravenous TCZ, highlighting the need to tailor treatment to patient response.[82]

The safety profile of TCZ in NIU aligns with its established use in rheumatologic conditions.[83–90] Common adverse events include infusion reactions, infections—particularly opportunistic infections—neutropenia, elevated liver enzymes, and hyperlipidemia.[48,91–93] Approximately 10% of patients in this systematic review discontinued TCZ due to adverse events.[46] Although the adverse event rate is relatively high, it highlights the necessity of proactive monitoring and timely intervention to mitigate risks. Regular assessment of inflammatory and immune markers improves treatment safety.[94,95] Recommended monitoring includes periodic complete blood counts with emphasis on

neutrophil levels; surveillance of C-reactive protein (CRP) to evaluate inflammation and treatment response; and serum IL-6 measurement in patients with systemic involvement for additional insights.[78] Upon detecting significant neutropenia or hepatic abnormalities, dose reduction or treatment interruption should be considered alongside infection prophylaxis and management of complications.[96–101] Intravenous infusions require medical supervision and slow infusion rates to minimize infusion reaction risks. In summary, comprehensive follow-up protocols and multidisciplinary collaboration—especially between rheumatology and ophthalmology—are essential to minimize TCZ-associated risks.[94]

This systematic review primarily relies on retrospective case reports and series, which inherently provide a lower level of evidence. The small sample sizes and lack of standardized controls introduce potential selection bias, as successful treatment cases are more likely to be published than failures, potentially leading to an overestimation of efficacy. Additionally, variability in follow-up durations across studies limits the ability to assess long-term efficacy and relapse rates adequately. Therefore, the reported 83.3% remission rate should be interpreted as a synthesis of current data pending confirmation by prospective randomized controlled trials. Logistic regression analysis further revealed that examined variables—etiology, uveitis type, and TCZ regimen—did not significantly influence the likelihood of a favorable TCZ response ($p > 0.05$). The McFadden R^2 value of 0.134 indicates these factors explain only a modest portion of outcome variability, suggesting other unmeasured factors affect TCZ efficacy in NIU. The retrospective design and limited sample size constrain the generalizability of these findings.

Future research should focus on evaluating TCZ efficacy within specific NIU subtypes, such as pediatric versus adult populations and NIU associated with systemic diseases, to better identify optimal candidates. Further studies are warranted to optimize treatment strategies, including combination therapies with other targeted agents, sequential or induction-maintenance regimens, and biomarker-guided personalized dosing. Large-scale, long-term cohort studies are essential to fully characterize TCZ's safety profile, especially regarding rare but severe adverse events. Beyond TCZ, investigations into novel IL-6/IL-6R inhibitors (eg, sarilumab) and modulators of related pathways (eg, JAK inhibitors) offer promising therapeutic alternatives for uveitis. These avenues will advance biologic treatment strategies for NIU, enhancing precision and efficacy.

Conclusion

The key conclusions of this systematic review are as follows: (1) TCZ, as an IL-6 receptor antagonist, shows promise as a safe and effective treatment option for NIU; (2) early initiation of TCZ after NIU diagnosis, alongside dynamic monitoring of neutrophil counts, CRP, and IL-6 levels, may enhance clinical outcomes, reduce relapse risk, and minimize adverse events; (3) further prospective, multicenter clinical trials are essential to establish optimal timing, dosing, and maintenance strategies for TCZ in NIU, thereby enabling evidence-based personalized therapy.

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