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REVIEW ARTICLE

Treating juvenile idiopathic arthritis (JIA)-related uveitis beyond TNF-α inhibition: a narrative review

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Abstract

Chronic anterior uveitis is the most frequent among extra-articular manifestations of juvenile idiopathic arthritis (JIA) and a relevant cause of ocular morbidity in children. Asymmetric arthritis, early onset disease, female sex, and anti-nuclear antibody (ANA) positivity are counted among risk factors for developing this complication. It usually has insidious onset and asymptomatic chronic-relapsing course, but the persistence of low-grade chronic inflammation can lead to irreversible structural ocular damage and to vision-threatening complications. For such reasons, achieving a complete absence of inflammation through early targeted and aggressive treatments is a primary therapeutic goal in these patients. This review is aimed at summarizing scientific evidence about biologic rescue therapy of JIA-related uveitis in patients who fail to achieve clinical remission, in spite of being treated with conventional disease-modifying anti-rheumatic drugs (cDMARDs) and at least one biologic tumor necrosis factor (TNF)-α inhibitor. Interleukin (IL)-6 inhibition appears a promising and safe option for refractory JIA-related uveitis. Abatacept and rituximab proved to be beneficial as well, but their efficacy together with some safety concerns needs to be more extensively evaluated.

Keywords Biologic therapy · Chronic anterior uveitis · Juvenile idiopathic arthritis · Rescue treatment

Background

Uveitis is a well-known vision-threatening complication of juvenile idiopathic arthritis (JIA) and is considered the most frequent among the extra-articular manifestations of the disease, with a mean frequency of 12–16% and a remarkable geographic variability. JIA-extended oligoarthritis course type is traditionally counted among risk factors for developing chronic anterior uveitis [1, 2]. Nevertheless, it is quite accepted among experts that a group of patients currently categorized in different JIA subtypes (oligoarticular persistent, oligoarticular extended, polyarticular seronegative, and psoriatic) shares a cluster of clinical features that strongly suggest a common background and a high risk for developing chronic anterior uveitis during the disease course: asymmetric arthritis, early onset disease, female predominance, frequent anti-nuclear antibody (ANA) positivity, and association with HLA-DR8 [3]. In this context, uveitis can precede the onset of arthritis in 3–7% of cases, but most patients develop ocular disease concomitantly or within the first 4 years after the occurrence of arthritis [4]. Though several forms of uveitis have been reported in association with JIA, the most common presentation is bilateral non-granulomatous anterior uveitis, characterized by insidious onset and asymptomatic chronic-relapsing course, leading to irreversible structural ocular damage [5]. The persistence of low-grade underlying active inflammation, even if clinical signs are absent, is associated with

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an increased risk of developing visual impairment over time, owing to the occurrence of structural complications as band keratopathy, posterior synechiae, cataract, glaucoma, hypotony, macular edema, epiretinal membrane, and optic disk edema [6–8]. Hence, all patients in whom a diagnosis of JIA is being considered should be screened for uveitis within 4–6 weeks from referral and then at 3–12-month intervals depending on risk stratification [9] (Table 1), and immunosuppressive therapy should be initiated without any delay when ocular inflammation is detected.

This review is aimed at summarizing scientific evidence about biologic rescue therapy of JIA-U in patients who fail to achieve clinical remission, in spite of being treated with cDMARDs and at least one biologic TNF-α inhibitor.

Methods

An extensive literature search in the MEDLINE database (via PubMed) has been performed up to December 2018. The following words were searched in Medical Subject Headings: "arthritis, juvenile rheumatoid" and "uveitis" or a number of synonyms of the previous ones ("jia" or "jra" or "juvenile" or "child" or "pediatric" or "paediatric" and "rheumatoid" or "rheumatic" or "idiopathic" or "chronic" or "systemic" and "arthritis" or "arthritides" or "polyarthritis" or "oligoarthritis" or "still's disease" or "still disease" and "paediatric" or "pediatric" or "child" or "juvenile" and "uveitis" or "iridocyclitis" or "vitritis" or "iritis" or "panuveitis" or "cyclitis" or "panuveitis") were searched as entree terms as well. Observational studies, clinical trials, case series, and reviews were carefully screened for eligibility in relation to the purpose of our manuscript. Papers were included if the outcome of any biological rescue treatment, both in children and in adults diagnosed with JIA-U refractory to TNF-α inhibition, was reported. Papers written in languages other than English, published before 2001, or not providing data about the main focus of this research were excluded. On the contrary, given the lack of randomized clinical trials and prospective studies, single case reports and short case series have been included in the literature review.

Tocilizumab

Tocilizumab is a fully humanized antibody that binds both to soluble and membrane-bound interleukin-6 (IL-6) receptors, inhibiting its pro-inflammatory effects. Several studies documented high levels of this cytokine in the vitreous fluid [10], in the aqueous humor [11–13], and also in the sera [14] of patients affected by non-infectious uveitis, suggesting the opportunity of targeting the IL-6 pathway in order to treat different clinical conditions such as chronic idiopathic uveitis, Vogt-Koyanagi-Harada syndrome, sarcoidosis, Behçet disease, HLA-B27-associated uveitis, and birdshot chorioretinopathy. Furthermore, IL-6 levels measured in the serum of rats affected by monophasic experimental autoimmune uveitis seem to positively correlate with clinical activity and histopathologic assessment of the disease [15].

Table 1 Frequency of follow-up visits according to the degree of risk of uveitis associated with JIA. Adapted from *Bou R 2015* [9]. *JIA* juvenile idiopathic arthritis, *RF* rheumatoid factor, *ANA* antinuclear antibodies

Oligoarticular JIA **RF – polyarticular JIA** **Psoriatic arthritis**	**ANA +**	Disease onset ≤6 years	Disease duration ≤4 years
			Disease duration 4-7 years
			Disease duration >7 years
		Disease onset >6 years	Disease duration ≤2 years
			Disease duration >2 years
	ANA –	Disease onset ≤6 years	Disease duration ≤4 years
			Disease duration >4 years
		Disease onset >6 years	
Systemic JIA **Enthesitis-related arthritis** **RF + polyarticular JIA**		HIGH RISK	every 3 months
		MODERATE RISK	every 6 months
		LOW RISK	every 12 months

IL-6 is a pleiotropic cytokine secreted by different cell lineages and displays a broad range of effects: it induces fever and production of acute phase reactants; it stimulates the differentiation of B lymphocyte in plasma cells and the activation of CD8+ cells in cytotoxic T cells; it promotes CD4+ T helper cell shift towards the Th17 subset rather than the T regulatory one [16]. The latter function, in particular, seems to play a significant role in the early phase of uveitis, suggesting interesting therapeutic opportunities centered on the IL-6–IL-17 pathway suppression [15, 17].

Tocilizumab appears the most promising biologic rescue treatment for JIA-U. It is administered by intravenous route, and doses usually adopted are the following: 8 mg/kg (max 800 mg) at 4-week intervals for patients at or above 30 kg weight, 10 mg/kg at 4-week intervals for patients less than 30 kg weight. The subcutaneous route of administration (162 mg every other week, followed by an increase to every week based on clinical response) is also reported in the treatment of JIA-U, with variable efficacy [18–20]. Concerning the safety profile, autoimmune cytopenia, increase in serum aminotransferases, gastrointestinal disorders, dizziness and nausea, allergic reactions, and increased risk of infections have been reported [16, 19].

The first report dealing with efficacy of tocilizumab in the treatment of JIA-U was provided by Tappeiner in 2012: he wrote about three adults with chronic anterior uveitis associated with vision-threatening complications, refractory to systemic steroid therapy, cDMARDs, and TNF-α inhibitors. The efficacy of tocilizumab was evaluated during a 6–12-month follow-up period. Clinical remission of uveitis and improvement of best-corrected visual acuity (BCVA) were obtained in two patients, while the third one showed no favorable response to the treatment [21]. Later, the same scientific group evaluated 17 children and young adults with severe course of persisting or refractory uveitis, treated with the IL-6 inhibitor, reporting a complete response in terms of uveitis inactivity in 10 patients after a mean of 5.7 months of treatment; furthermore, systemic glucocorticoids or cDMARDs could be spared in seven patients [22]. The multicenter study conducted by Calvo-Rìo evaluated the largest cohort of patients affected by severe JIA-U administered with tocilizumab, after the failure of cDMARDs and one to five different biologic agents. The authors disclosed a favorable clinical response to the anti-IL-6 treatment in 19 out of 25 patients, who achieved remission of uveitis at a median follow-up of 12 months; as secondary outcomes, significant reduction of prednisone dose and improvement of BCVA were also attained; nine patients who showed uveitic macular edema at baseline showed a statistically significant decrease in central foveal thickness (CFT) measured by OCT at the 12-month evaluation [19]. The efficacy of the inhibition of IL-6 activity in the treatment of patients affected by JIA and uveitic macular edema was reported also in other case series, suggesting tocilizumab as a promising therapeutic option for this complication [22–26]. Similarly, Adàn published a case report of a secondary retinal vasoproliferative tumor in a 29-year-old female with a long history of JIA-U, refractory to methotrexate, infliximab, and adalimumab. After 12 administrations of tocilizumab, the ophthalmic examination revealed a distinct regression of the tumoral mass at OCT and a significant improvement of BCVA [27]. Further case reports and case series are available in the literature, and they mostly validate the previously presented evidences [20, 28–32] (Table 2).

Abatacept

Abatacept is a fully human soluble fusion protein composed of two domains: the extracellular portion of cytotoxic T lymphocyte antigen 4 (CTLA-4) and a modified FC domain of immunoglobulin G1 (IgG1). The first domain binds to the costimulatory signals CD80 or CD86 on antigen presenting cells, acting as a competitor of their natural binding molecule CD28 on T cells. This interference selectively inhibits T cell activation, with consequences on many downstream cytokine pathways involved in the pathogenesis of autoimmune diseases [33]. Although not completely clarified, the role of T lymphocytes in the development of endogenous uveitis and JIA has been extensively studied [34–36]. The blockade of CD28-CD80/86 costimulation in experimental models of induced autoimmune anterior uveitis and uveoretinitis interfered with effector T cell generation, inhibited TNF-α production, and finally prevented the development of the autoimmune ocular disease [37, 38].

Abatacept has been licensed for intravenous use in patients affected by rheumatoid arthritis, psoriatic arthritis, and polyarticular JIA refractory to TNF-α inhibitors in Europe. The suggested dosage is 10 mg/kg (max 1000 mg) at 0–2–4 weeks and every 4 weeks thereafter. Abatacept administration is generally safe and well tolerated [33], sometimes associated to mild to moderate adverse events, such as nasopharyngitis, upper respiratory tract infections, vomiting, pyrexia, or acute infusion reactions of single occurrence and not requiring premedication; nevertheless, severe infections have been reported with a lower frequency [39]. In regard with abatacept use in children with JIA-U, post-infusion headache, weight gain, skin reactions, anaphylaxis, oral mycosis, and arthritis flare in one patient have been specifically reported [29, 40, 41].

Since the first patient with a sustained recovery from active JIA-U on abatacept treatment was reported [42], analogue attempts were made in patients refractory to TNF-α inhibitors, with variable results in terms of clinical efficacy and steroid-sparing effect [19, 21, 23–25, 29, 30, 40–46] (Table 3). A multinational retrospective study conducted by Birolo collected 31 patients affected by severe JIA-U, comparing abatacept as first-line biologic therapy ($N = 14$) and as a rescue treatment ($N = 17$); the costimulation inhibitor allowed patients to be free from new uveitis flares for more than 6 months in 17

Table 2 Tocilizumab in JIA-associated uveitis: data gathered from current available literature

First author, year [ref.]	LoE	Dosage employed	Num. Of JIA patients	Outcome measures	Results	Follow-up (months)	Safety
Calvo-Río V 2017 [19]	IIB	8 mg/kg IV every 4 weeks ($n = 21$), every 2 weeks ($n = 2$) or every 8 weeks ($n = 1$) or 2.9 mg/kg SC every week ($n = 1$)	25	(1) Clinical remission of uveitis (2) Tapering of prednisone	(1) 19/25 (2) 25/25	5.5–24	- 2 thrombocytopenia - 1 autoimmune anemia - 1 pneumonia - 1 viral conjunctivitis - 1 bullous impetigo
Tappeiner C 2016 [22]	IIB	8 mg/kg IV every 4 weeks	17	(1) Clinical remission of uveitis (2) BCVA (3) Sparing of other therapies	(1) 10/17 (2) 2/17 (3) 7/17	3–12	None
Quesada-Masachs E 2017 [18]	IV	(1) 8 mg/kg IV at 2–4-week intervals (2) 162 mg/week SC or adjusted to body surface area	4	Maintenance of clinical remission of uveitis after switching from IV to SC route	(1) IV 4/4 (2) SC 1/4	5–7	None
Mesquida M 2018 [24]	IV	8 mg/kg IV at 4-week intervals	6	(1) Regression of macular edema (decrease in Central Foveal Thickness measured by OCT) (2) BCVA (3) Evidence of active inflammation	(1) 6/6 (2) 6/6 (3) 4/6	24–48	- 1 pneumonia - 1 neutropenia
Silpa-Archa S 2016 [28]	IV	4 or 8 mg/kg IV at 2–4-week intervals	5	(1) Clinical remission of uveitis	(1) 2/5	4–29	- 1 dizziness and nausea
Tappeiner C 2012 [21]	IV	8 mg/kg IV at 4-week intervals	3	(1) Clinical remission of uveitis (2) Sparing of other therapies	(1) 2/3 (2) 0/3	6–12	None
Tsang AC 2014 [29]	V	8 mg/kg IV at 2–4-week intervals	1	(1) Clinical remission of uveitis (2) Sparing of other therapies	(1) 1/1 (2) 1/1	12	- 1 neutropenia
Adán A 2014 [27]	V	8 mg/kg IV	1	(1) Regression of retinal vasoproliferative tumor (2) BCVA	(1) 1/1 (2) 1/1	12	None
Adán A 2013 [25]	V	8 mg/kg IV at 4-week intervals	1	(1) Regression of cystoid macular edema (decrease in Central Foveal Thickness measured by OCT) (2) BCVA (3) Evidence of active inflammation	(1) 1/1 (2) 1/1 (3) 1/1	7	None
Deuter CME 2017 [26]	IV	8 mg/kg IV at 4-week intervals	2	(1) Regression of macular edema (decrease in Central Foveal Thickness measured by OCT) (2) BCVA (3) Evidence of active inflammation	(1) 2/2 (2) 2/2 (3) 2/2	20–35	None
Mesquida M 2014 [23]	IIB	8 mg/kg IV at 4-week intervals	3	(1) Regression of macular edema (decrease in Central Foveal Thickness measured by OCT) (2) BCVA (3) Evidence of active inflammation	(1) 3/3 (2) 3/3 (3) 3/3	14–18	None
Souto FM 2018 [31]	V	–	1	Efficacy	0/1	–	–
Salek SS 2018 [32]	V	162 mg/week SC	1	Efficacy	0/1	10	–
Breitbach M 2017 [30]	IV	–	3	Uveitis inactivity	2/3	–	–

JIA juvenile idiopathic arthritis, *IV* intravenous administration, *SC* subcutaneous administration, *BCVA* best corrected visual acuity, *OCT* optical coherent tomography, *LoE* level of evidence

Table 3 Abatacept in JIA-associated uveitis: data gathered from current available literature

First author, year [ref.]	LoE	Dosage employed	Number of JIA patients	Outcome measures	Results	Follow-up (months)	Safety
Angeles-Han 2008 [42]	V	10 mg/kg IV at week 0–2–4 and every 4 weeks thereafter	1	(1) Clinical remission of uveitis (2) Tapering of other therapies	(1) 1/1 (2) 1/1	18	None
Birolo C 2016 [40]	IIB	–	31 • 14 first line • 17 second line	Clinical remission of uveitis (absence of flares for more than 6 months)	17/31 No difference according to biologic line	12	- 1 post-infusion headache - 1 weight gain
Alpigiani MG 2010 [43]	V	750 mg IV at week 0–2–4 and every 4 weeks thereafter	1	–	Partial improvement	–	None
Elhai M 2011 [44]	IV	10 mg/kg IV at week 0–2–4 and every 4 weeks thereafter	2	(1) Clinical remission of uveitis (2) Tapering of other therapies	(1) 2/2 (2) 1/2	10–16	None
Kenawy N 2011 [45]	IV	500 mg IV at week 0–2–4 and every 4 weeks thereafter	2	Clinical remission of uveitis	2/2	12	–
Tappeiner C 2015 [46]	IIB	10 mg/kg (max 750 mg) IV at week 0–2–4 and every 4 weeks thereafter	21	(1) Clinical remission of uveitis (2) Tapering of other therapies	(1) 11/21, but only 3/11 were on clinical remission at last visit (2) 3/21, but unsuccessfully	12	None
Zulian F 2010 [41]	IIB	10 mg/kg (max 750 mg) IV at week 0–2–4 and every 4 weeks thereafter	7	(1) Clinical remission of uveitis (2) Tapering of steroids	(1) 7/7 (2) 4/4	3–11	- 1 skin reactions, oral mycosis and arthritis flare
Breitbach M 2017 [30]	IV	–	2	Uveitis inactivity	1/2	–	–
Adán A 2013 [25]	V	–	1	Regression of cystoid macular edema (decrease in Central Foveal Thickness measured by OCT)	0/1	–	–
Calvo-Río V 2017 [19]	IV	10 mg/kg IV at week 0–2–6 and every 8 weeks thereafter	6	Clinical remission of uveitis	0/6	–	–
Mesquida M 2014 [23]	V	–	1	Regression of macular edema (decrease in Central Foveal Thickness measured by OCT)	0/1	–	–
Mesquida M 2018 [24]	IV	–	2	Regression of macular edema (decrease in Central Foveal Thickness measured by OCT)	0/2	–	–
Tappeiner C 2012 [21]	V	10 mg/kg at 4-week intervals	1	Clinical remission of uveitis	0/1	–	–
Tsang AC 2014 [29]	V	500 mg IV at week 0–2–4 and every 4 weeks thereafter	1	Clinical remission of uveitis	1/1	3	- 1 anaphylactic reaction

JIA juvenile idiopathic arthritis, *IV* intravenous administration, *OCT* optical coherent tomography, *LoE* level of evidence

out of 31 cases, with no significative difference between the two study groups [40]. Another retrospective evaluation of abatacept's efficacy was performed by the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC) in a cohort of 21 children with resistant JIA-U (and vision-threatening complications in 17 of them); patients underwent ophthalmological controls every 3 months for 1 year, and 11 of them (52.4%) were found on clinical remission during at least one follow-up visit. Nevertheless, a new exacerbation of the disease was detected in eight patients during the follow-up and, furthermore, attempts of tapering concomitant systemic and local treatments were not successful in most cases [46]. More favorable results had been attained otherwise by the Italian group led by Zulian in 2010 on seven children administered with abatacept because of their refractory sight-threatening chronic anterior JIA-U and prospectively evaluated: in all of them, a 2-degree decrease or disappearance of inflammation (anterior chamber cells) was obtained in the first 6 months of therapy. Four patients were able to withdraw or reduce by half systemic glucocorticoid therapy. No new structural complications were detected during a follow-up period of 7 to 11 months, while the pre-existing ones (band keratopathy, posterior synechiae, cataract, vitritis, posterior vitreal detachment, and cystoid macular edema) remained substantially stable [41]. Interestingly, in a small case series published by Elhai, the efficacy of abatacept on disease control was not compromised when the intervals between administrations were widened, respectively, to 6 and 7 weeks apart [44]. A clinical trial on abatacept safety profile and efficacy in non-infectious uveitis has been recently completed (ClinicalTrials.gov Identifier: NCT01279954).

Rituximab

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed towards CD20 antigen of mature B cells and it was initially developed for the treatment of lymphoproliferative disorders. Its immune-modulating effect has been proven to be nevertheless beneficial in many autoimmune conditions, including rheumatoid arthritis, immune-mediated cytopenias, neurologic disorders, systemic lupus erythematosus, granulomatosis with polyangiitis, and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis [47]. Recent studies on circulating blood mononuclear cell gene expression profile disclosed a significant upregulation of B cell receptor signaling pathways in patients with JIA affected by the persistent oligoarticular type, as the strong correlation of this clinical subset of JIA with ANA positivity clearly suggests [48]. B cells targeted by rituximab are marked for destruction through antibody-dependent cell-mediated cytotoxicity, complement-mediated lysis, growth inhibition, or direct induction of apoptosis [49]. CD20 antigen is expressed on the surface of mature B lymphocytes, but neither on plasma cells nor on B lineage precursor stem cells, preserving immunoglobulin levels and ensuring a transient depletion of the circulating B compartment, including self-reactive lymphocytes [50]. It modulates also T cell response, promoting the differentiation of T regulatory cells [51, 52], not only as a consequence of B cell depletion and shift of their antigen-presenting function to dendritic cells and macrophages, but also directly by targeting subsets of T cells that produce pro-inflammatory cytokines and express low levels of CD20 or a cross-reacting antigen [53].

Rituximab is administered by intravenous route and different posologic regimens are adopted, according to diverse drug registration dosage schemes: 375 mg/mq, 500 mg/mq, 600 mg/mq, 1000 mg, or 500 mg on days 1 and 15 and recall infusions, if necessary (Table 4). No adverse events associated with rituximab are reported in literature in patients affected by JIA-U; nevertheless, in studies carried out on patients with rheumatoid arthritis [58] and non-Hodgkin's lymphoma [59], mild-to-moderate infusion-related reactions (IRR) and less frequently anaphylaxis have been experienced during the first infusion of rituximab; the probability of infusion-related adverse events is higher in patients affected by lymphoma than in those with rheumatoid arthritis and decreases in both groups during subsequent administrations of the drug. Anyway, in order to prevent and reduce the severity of IRR, methylprednisolone, paracetamol, and antihistamines are commonly given before rituximab administration [www.ema.europa.eu]. As concerns the risk of infectious complications, they have been reported as being low, due to the stability of mean serum immunoglobulin levels [59].

CD20 antigen has been targeted in small cohorts of patients with refractory JIA-U, showing interesting results [54–56]. Conversely, other anecdotal reports achieved less favorable outcomes [19, 20, 24]. A retrospective multicenter case series conducted by Heiligenhaus evaluated the clinical outcome of ten patients with severe JIA-U with vision-threatening complications and active arthritis, who underwent two infusions of rituximab 375 mg/m^2, after the failure of topical and systemic glucocorticoids, cDMARDs, and at least one TNF-α inhibitor. Uveitis improved in seven patients affected by ANA+ oligoarthritis, who succeeded in tapering down topical glucocorticoids and cDMARDs during a follow-up period of 7–18 months. New uveitis relapses occurred in four of the seven responders after 6–9 months and were attributed to the restoration of peripheral blood CD20 cells, but were successfully suppressed through a recall infusion of rituximab in all but one case. Uveitis activity persisted after rituximab treatment in three patients, suggesting a major role of long lived plasma cells as predominant producers of the autoantibodies in that subset of patients [54]. Valuable results have been obtained by Miserocchi, who managed eight patients with JIA-U, treated with rituximab 1000 mg for a mean period of 12 months after failure of three different TNF-α inhibitors. At the last follow-

Table 4 Rituximab in JIA-associated uveitis: data gathered from current available literature

First author, year [ref.]	LoE	Dosage employed	Num. of JIA patients	Outcome measures	Results	Follow-up (months)	Safety
Heiligenhaus A 2011 [54]	IV	375 mg/m^2 IV 2 infusions at 2-week intervals	10	(1) Clinical remission of uveitis (2) Tapering of other therapies	(1) 7/10 (2) 7/10	7–18	None
Miserocchi E 2011 [55]	IV	1 g IV on days 1 and 15 and recall infusions at 12 and 21 months	8	(1) Clinical remission of uveitis (2) Tapering of other therapies	(1) 7/8 (2) 8/8	7–25	None
Miserocchi E 2016 [56]	IV	1 g IV on days 1 and 15 and every 6 months thereafter if necessary	8	(1) Clinical remission of uveitis (2) Tapering of other therapies	(1) 8/8 (2) 8/8	26–62	None
Angeles-Han S 2008 [42]	V	600 mg/m^2 IV	1	Clinical remission of uveitis	Secondary inefficacy after 6 months	6	–
Breitbach M 2017 [30]	V	–	1	Uveitis inactivity	1/1	–	–
Curragh DS 2018 [20]	IV	500 mg IV	2	Uveitis inactivity	0/2	6–12	–
Pelegrin L 2014 [57]	V	1 g IV on days 1 and 15 and every 6 months thereafter	1	(1) BCVA (2) Clinical improvement (3) Tapering of other therapies	(1) 1/1 (2) 1/1 short-lived (3) 0/1	5	–
Adán A 2013 [25]	V	–	1	Regression of cystoid macular edema (decrease in Central Foveal Thickness measured by OCT)	0/1	–	–
Calvo-Río V 2017 [19]	IV	1 g IV on days 1 and 15 (single course)	2	Clinical remission of uveitis	0/2	–	–
Mesquida M 2018 [24]	IV	–	2	Regression of macular edema (decrease in Central Foveal Thickness measured by OCT)	0/2	–	–
Tsang AC 2014 [29]	V	500 mg/m^2 IV at 2-week intervals	1	Clinical remission of uveitis	0/1	6	–

JIA juvenile idiopathic arthritis, *IV* intravenous administration, *BCVA* best corrected visual acuity, *OCT* optical coherent tomography, *LoE* level of evidence

up assessment, seven of them achieved complete control of intraocular inflammation and were on persistent clinical remission, having withdrawn or tapered down the concomitant cDMARDs [55]. The same group published another analog series of eight patients affected by longstanding and refractory JIA-U in which rituximab allowed maintaining uveitis inactivity for a longer follow-up (26–62 months), with a considerable sparing of concomitant immunosuppressant medications. It is worth mentioning that two patients discontinued rituximab after 29 and 26 months because of lack of efficacy on arthritis, and that they were switched to golimumab [56]. Other papers available in the medical literature [25, 29, 30, 42, 57] mention more or less successful courses of the anti-CD20 monoclonal antibody rituximab for the treatment of refractory JIA-U, as listed in Table 4.

Others

Daclizumab is a humanized IgG monoclonal antibody produced by recombinant DNA technology, which targets CD25, the α-chain of the IL-2 receptor, expressed on the surface of human T lymphocytes once activated by mitogens or antigens, blocking the proliferative signal of this cytokine. As evaluated in experimental models of autoimmune uveoretinitis in the monkey, it significantly inhibits the IL-2-driven expansion of activated T cells and subsequently the development of the autoimmune ocular disease [60]. Intravenous daclizumab has been considered a promising rescue treatment for refractory non-infectious uveitis in childhood, since it had beneficial effects both on ocular inflammation and visual acuity at low dosage (1 mg/kg at 2–8-week intervals) [61]. In a 2009 pilot study, it led to a two-step reduction of anterior chamber inflammation within 12 weeks in four out of six patients with JIA-U when administered at high dose (8 mg/kg at baseline, followed by 4 mg/kg at week 2 and 2 mg/kg every 4 weeks thereafter). Nevertheless, the authors expressed the need for more extensive studies focusing on the safety profile associated with high-dose protocols [62]. Other papers reported that intravenous or subcutaneous daclizumab could effectively control the activity of severe intermediate and posterior non-infectious uveitis in 67–80% of adult patients, with a considerable steroid-sparing effect [63, 64]. However, daclizumab has been discontinued by the manufacturer in 2018 due to severe safety concerns related to the central nervous system [www.aifa.gov.it/sites/default/files/Zinbryta_DHPC_ITA_12-03-2018].

A rising interest on the efficacy of interleukin (IL)-1 blockers in several different inflammatory ocular diseases [65] has encouraged their employment also in pediatric patients affected by refractory JIA-U. A young girl with severe JIA-U, cataract, and cystoid macular edema, refractory to anti-TNF-α and abatacept, was treated with the IL-1beta monoclonal antagonist canakinumab (2 mg/kg every 4 weeks by subcutaneous injection) and concomitantly with oral prednisone and methotrexate; a 12-month follow-up showed both ocular remission and visual acuity recovery, in association with successful withdrawal of co-treatments [66]. On the other hand, further case reports have mentioned the use of the IL-1 receptor antagonist anakinra in patients affected by JIA-U [19, 24, 54].

The pathogenetic role of the IL-23/IL-17 axis has been studied both in experimental models of non-infectious uveitis and in several autoimmune systemic or ocular disorders [67, 68]. As concerning JIA, experimental evidences support a direct correlation between the number of peripheral Th17 cells and disease activity, to a point that a higher Th17 level predicts a longer period to reach remission [69]. A clinical report of an effective treatment with ustekinumab, the monoclonal antibody directed against IL-12 and IL-23, in a child with uveitis and ANA+ HLA-B27+ juvenile psoriatic extended oligoarthritis has been recently published by Salek: the patient was affected by anterior and intermediate uveitis since the age of four and was treated with systemic glucocorticoids, methotrexate, infliximab, and adalimumab. The introduction of ustekinumab 45 mg every 3 weeks allowed control of intraocular inflammation [32]. No other data about ustekinumab in JIA-U are currently available in the medical literature.

Conclusive remarks

Consensus-based recommendations for the management of JIA-U have been recently developed by an experts' group from the Single Hub and Access point for Pediatric Rheumatology in Europe (SHARE), with the purpose of overcoming the previous heterogeneity of clinical and scientific approach to anterior uveitis, a well-known vision-threatening complication occurring in children with JIA [70]. According to the recommendations, early introduction of methotrexate (MTX) is recommended if poor prognostic factors are present at the first evaluation or if uveitis inactivity is not reached in 3 months of topical glucocorticoids, to avoid the development of cataract and glaucoma [70]. In recent years, the importance of complete absence of inflammation as a primary therapeutic target in JIA patients has been extended also to the extra-articular manifestations of the disease [71]. Also, in regard of JIA-associated uveitis (JIA-U), the traditional step ladder treatment approach is being replaced by top-down algorithms, in which systemic management is started as soon as needed at the highest tolerated levels, in order to attain complete control of inflammation and to prevent or minimize the possibility of vision-threatening complications [8, 72]. Therefore, when conventional disease-modifying anti-rheumatic drugs (cDMARDs) fail to control ocular inflammation, switching or adding one tumor necrosis factor (TNF)-inhibitor agent is recommended [73]. On the basis of several cohort studies [74] and one randomized controlled trial [75], adalimumab is the biologic agent with the strongest scientific evidence of

efficacy in JIA-U, when administered in association with MTX, infliximab is regarded as second choice, while etanercept should not be considered for these patients.

If the role of anti-TNF-α agents as first-line biologic drugs in patients with uveitis resistant to cDMARDs has reached a unanimous level of agreement among rheumatologists and ophthalmologists [73], variegate data are available in the medical literature about rescue solutions to manage anti-TNF-α failure in clinical practice. Experts' opinion suggests testing anti-drug antibodies and drug trough level, and eventually increasing anti-TNF-α dosage or shortening intervals between administrations [76–78]. Furthermore, some data derived from descriptive studies suggest that also switching between different anti-TNF-α agents can be a reasonable strategy in order to achieve ocular remission [79, 80].

We have herein reviewed all scientific evidence about biologic drugs which can be considered as rescue therapy in managing children with severe refractory JIA-U. We noticed, even so, some critical issues, such as the lack of randomized controlled trials and comparative studies, the relatively small sample size of cohorts studied, and an overall heterogeneity of protocols and dosages employed, which make any effort to compare these results definitely unreliable. Taken into account the previously mentioned limitations, IL-6 inhibition appears a promising and safe option for these patients, also when vision-threatening macular edema complicates uveitis. In this regard, a multicenter phase II trial protocol of tocilizumab associated with methotrexate in anti-TNF-α refractory patients with JIA-U (the APTITUDE trial) is ongoing in the UK and is expected to end on April 2019 [https://doi.org/10.1186/ISRCTN95363507]. Abatacept proved to be beneficial in some study cohorts as well, and long-term outcome assessments would be desirable. Moreover, interesting data have been published on the anti-CD20 monoclonal antibody rituximab for resistant uveitis in JIA, but its efficacy together with some safety concerns related to the intravenous infusion of the drug need to be more extensively evaluated. A consistent effort to clarify the pathogenetic fundamentals of JIA-U and to identify reliable biomarkers of this challenging condition is necessary to identify higher-risk patients at an early stage of the disease and promptly address them to more-targeted and aggressive therapies.

Compliance with ethical standards

Disclosures None.

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