Review
Future Rheumatology

New developments in the management of juvenile idiopathic arthritis-related uveitis

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Chronic anterior uveitis is the most important extra-articular complication of juvenile idiopathic arthritis. It is more frequent in the early-onset forms, with a higher prevalence in the oligoarticular subtype, and bilateral in most cases. The risk for visual impairment is still relevant due to sight-threatening complications, such as band keratopathy, cataract, glaucoma and cystoid macular edema. To date, treatment is not standardized and involves a complex decision-making process. Among several steroid-sparing immunosuppressive options, low-dose methotrexate is still the most diffuse treatment. Mycophenolate mofetil is another potential choice, although it is less effective in chronic anterior uveitis than in posterior or intermediate uveitis. TNF-α antagonists, the new generation of agents increasingly frequently used in autoimmune and rheumatic conditions, have demonstrated effectiveness in open-label studies, although no large, randomized, controlled trials have been reported so far. Although infliximab, an anti-TNF monoclonal antibody, seems to be superior to etanercept, an anti-TNF receptor antagonist, in controlling intra-ocular inflammation, serious side effects and loss of efficacy after the first year of treatment are reported. Adalimumab has evidenced efficacy similar to infliximab, but a better tolerance. In this review, the current practice in the medical management of juvenile idiopathic arthritis-related uveitis and the potential new agents are discussed.

New treatments of juvenile idiopathic arthritis-related uveitis

Juvenile idiopathic arthritis (JIA)-related uveitis accounts for the majority of noninfectious anterior uveitis among children [1], and represents one of the major sight-threatening challenges in the pediatric age [2].

Chronic anterior uveitis (CAU) is the most important extra-articular complication of JIA. It is more frequent in the early-onset forms, with a significant difference between the oligoarticular (40%) and polyarticular (14%) subtype. The most severe forms, approximately a third of the cases, can be complicated by synechiae (21.8%), band keratopathy (14.1%), cataract (23.2%), glaucoma (15.5%), cystoid macular edema (CME; 4.9%) and consequent visual deterioration. However, in the more recent studies, a decreased prevalence of severe visual impairment has been registered [3].

The final outcome is related to many factors: JIA subtype, diagnostic delay, age at onset, disease duration and treatment. In a large cohort of 760 patients with JIA, uveitis developed in 74 (9.3%) within the first 4 years following the diagnosis of arthritis in most of the cases, with a mean time interval of 21 months since arthritis onset [4].

The ocular inflammation is usually insidious and asymptomatic. For this reason, when uveitis precedes arthritis, the visual prognosis is often severe, owing to the delay in diagnosis. In a retrospective study, we observed that the time interval, in months, between the onset of arthritis and the first uveitis, and elevated α_2-globulins at onset of arthritis, were the most significant variables to predict a severe uveitis course in JIA [5].

In most cases, uveitis is bilateral; if unilateral, progression towards the controlateral side is observed within the first 12 months. In JIA, uveitis develops within 1, 2 and 4 years after arthritis in 73, 77 and 90%, respectively. CAU is the most common anatomic type of uveitis (83%), with development of complications in approximately half of the cases within 5 years after diagnosis [6]. When already present at the first visit, complications are more frequent, while antinuclear antibodies (ANA) positivity doesn't seem to be a predictor for uveitis severity.

Treatment

Currently, the treatment of CAU is non-standardized and involves a complex decision-making process. The lack of randomized, controlled clinical trials on pharmacological approaches for uveitis is another crucial point.

Keywords
anti-TNF ■ JIA ■ juvenile idiopathic arthritis ■ treatment ■ uveitis

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Despite the considerable improvement in the therapy of arthritis, less progress has been made in the treatment of persistent uveitis, which remains one of the greatest challenges encountered by pediatric rheumatologists and ophthalmologists.

Since an early aggressive disease control is advocated in many chronic inflammatory disorders, a similar approach should also be adopted for CAU in view of preserving visual function and preventing serious complications [7].

Initial and more traditional therapy includes topical, oral and/or subtenon or orbital-floor injected glucocorticoids.

Topical medication

Topical medication, consisting of corticosteroid eyedrops in combination with cycloplegic agents, is the first step in the treatment of CAU. Topical steroid and cycloplegic drops, although effective, often have limited compliance, especially if their use is required frequently and in early infancy.

At the best of our knowledge, after the study of Chylack and colleagues, reporting a failure rate in almost a third of the patients within 6 months of treatment with topical corticosteroids [8], no other studies have been reported.

Peribulbar steroid injections

The use of peribulbar steroid injections has been suggested for the treatment of severe unilateral CAU with vitreitis or CME [9]. A nonrandomized prospective study, comparing safety and efficacy of posterior subtenon injection of triamcinolone acetonide with orbital-floor injection of methylpredisolone acetate in posterior uveitis, showed no significant difference as far as improvement rate between the two groups [10]. However, lid ptosis occurred only in the triamcinolone-treated group. Although both techniques seem to be effective, injections of glucocorticoids are quite invasive and, especially in children, should be performed under general anesthesia.

Intravitreal steroid injections

Intravitreal steroid injections represent another possible treatment option, especially for CME. Safety and efficacy of this approach has been recently evaluated in a group of children with CME secondary to noninfectious and JIA-related uveitis. Following treatment with intravitreal triamcinolone acetonide (2 or 4 mg), resolution of CME was achieved in all eyes, but visual acuity significantly improved in only half of them. The most important adverse events were elevated intra-ocular pressure (31%), and rapid progression of cataract (55%) [11,12]. Owing to these side-effects and to the invasive technique, this treatment should be performed only in very selected cases.

Systemic treatment

It is well known that parenteral and oral therapy with glucocorticoids is quite effective in reducing ocular inflammation in approximately two-thirds of the patients [13]. Unfortunately, this treatment cannot be long-lasting because of the well known side effects consisting in longitudinal growth failure, weight gain, osteoporosis, pancreatitis, diabetes mellitus and hypertension. Indeed, glucocorticoids themselves may contribute to the development of glaucoma and cataract in children. In view of these side effects and of the unpredictable outcome of cataract surgery (Figures 1 & 2) in patients with CAU [14], methotrexate (MTX) and ciclosporin A (CyA) have been introduced as steroid-sparing agents [15].

This treatment is largely derived from protocols developed for life-threatening conditions such as lymphoid malignancies, solid organ transplants and systemic vasculitis. The central role of the T cells, as shown in animal models of uveitis or, occasionally, in pathological specimens of human uveitis, has convinced many physicians to use other antimetabolite or antiproliferative agents (e.g., azathioprine or mycophenolate mofetil), calcineurin inhibitors (e.g., CyA and tacrolimus), and more recently, a variety of anticytokines agents (monoclonal antibodies or receptor antagonists) (Table 1 & 2).

Methotrexate

Methotrexate, an antimetabolite with a long track record for the treatment of uveitis [16], is commonly used as a first-line steroid-sparing agent. Its ability to achieve control of intraocular inflammation in CAU ranges from 45 to 72.6%, depending on the definition of inflammation and length of follow-up [17–20]. Low-dose MTX (7.5–15 mg/m^2/week) has been considered the treatment of choice of CAU resistant to topical corticosteroids. Recognized as effective in the treatment of JIA, MTX efficacy has also been confirmed in the treatment of JIA-associated uveitis, although only in small, uncontrolled case studies [21,22]. Conversely, a report on 11 patients with CAU showed that the addition of MTX to the treatment regimen did not result in a complete control of the inflammation, nor reduced the corticosteroid need and the number of relapses in nearly half

of the patients [23]. Recently, the efficacy of MTX as a single systemic immunosuppressive drug, and the requirement for additional anti-inflammatory agents, has been evaluated in 35 patients with severe chronic JIA-related uveitis, with ocular complications present before treatment in most of them (88.5%). During a mean follow-up of 27.6 months, quiescence of uveitis was obtained in 70% of the patients, without topical steroids in only 11%. Additional systemic immunosuppressive drugs were required in two patients [24]. To date, controlled studies comparing efficacy of early versus late MTX treatment, in JIA-related uveitis, have not been reported.

Ciclosporin A

Ciclosporin A has been proposed as an effective alternative to MTX in selected pediatric cases of cortico-resistant chronic uveitis [25]. According to uncontrolled clinical studies, CyA has evidenced efficacy in several types of uveitis, either used alone, at a daily dose of 5–10 mg/kg/day, or, at lower doses, in association with other immunosuppressive drugs [26]. The reported response rate ranges between 82 [27] and 50% [28]. Unfortunately, the only prospective clinical trial in JIA, using CyA at a dose of 3–5 mg/kg/day, did not show clear-cut benefits compared with standard treatment [29].

In a recent multicenter retrospective study, the efficacy of CyA as monotherapy or in combination with corticosteroids or MTX was evaluated in a cohort of 82 children with JIA [30]. A complete control of uveitis, during a mean follow up of 3.9 years, was obtained with CyA monotherapy, at a mean dosage of 2.9 mg/kg/day in 24% of the patients. When CyA was combined with MTX, efficacy was raised up to 48.6% of patients. Unfortunately, pre-existing CME did not resolve in any of the patients.

Other agents, such as azathioprine, clorambucil or cyclophosphamide, occasionally utilized when CyA was ineffective or not tolerated, showed partial and short-lasting efficacy and led to a greater risk of side effects [15].

Mycophenolate mofetil

In 1995, an experimental study demonstrated that mophetyl-micophenolate (MMF), a purinic metabolism inhibitor, prevented the development of the antigen S-induced autoimmune uveitis in mice [31]. More recently, MMF, used alone or in combination with CyA, has been found to be effective for the treatment of some patients with autoimmune ocular diseases, such as cicatricial pemphigoid, or corneal transplant rejection [32]. In 1999, a prospective uncontrolled pilot study showed that MMF, used at a dose of 2 g/day, alone or in combination with corticosteroids or CyA, controlled the inflammation in ten out of 11 adult cases, most with intermediate or panuveitis, with acceptable side effects [33]. Several further studies have confirmed the efficacy of MMF in reducing

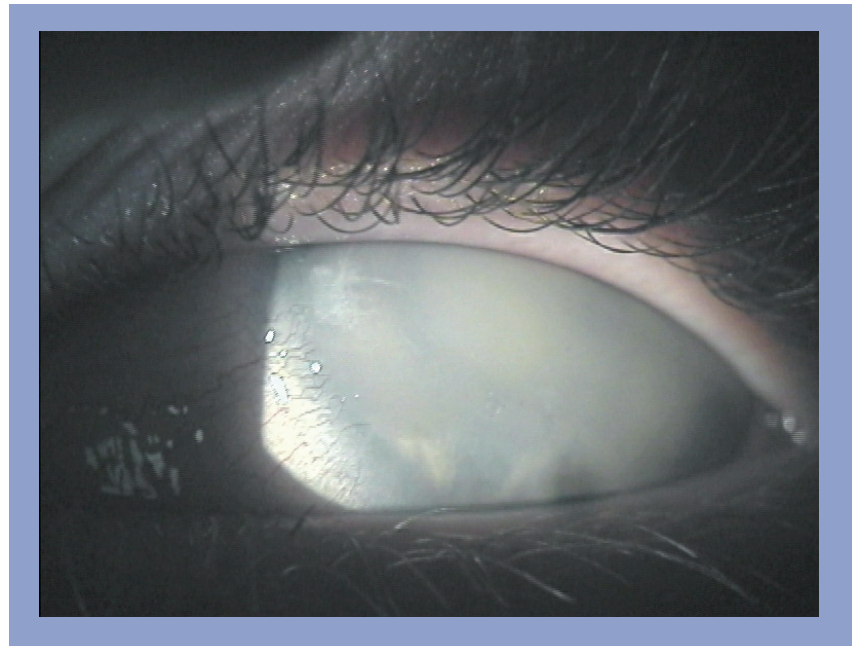

Figure 1. Left eye: Corneal leucoma following cataract surgery (first operated eye) in a child with juvenile idiopathic arthritis – uveitis.

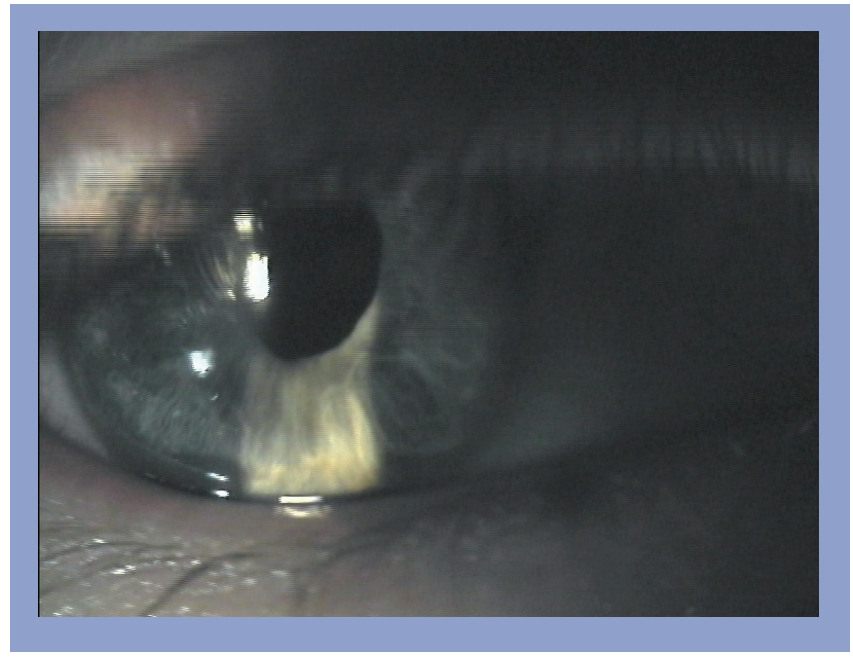

Figure 2. Right eye: Remitted uveitis following cataract surgery (second operated eye) in the same child on anti-TNF-α therapy.

Table 1. Immunosuppressive agents: main properties and side effects.

Agent	Structure	Route of administration	Dose range	Main side effects
Methotrexate	Folic acid analogue, inhibitor of dihydrofolate reductase	Oral or parenteral (sc. or im.)	10–30 mg/m²/week max 1 mg/kg/week	Nausea, vomiting, dyspepsia, hepatotoxicity; injection site reactions
Ciclosporin	Cyclic peptide inhibiting T lymphocyte proliferation	Oral (suspension or capsules)	2–5 mg/kg/day (two divided doses)	Hirsutism, hypertension, renal insufficiency, nausea, vomiting and gingival hypertrophy
Mophetil-mycophenolate	Purinic metabolism inhibitor	Oral (capsules)	0.5–1 g/m²/day (in two divided doses)	Nausea, vomiting, dyspepsia, diarrhea
Cyclophosphamide	Alkylating agent	Oral or iv.	Oral 0.5–2 mg/kg/day; iv. 0.5–0.75 g/m² (max 1 g) monthly pulse	Leukocytopenia, thrombocytopaenia, cystitis, alopecia, inappropriate ADH secretion syndrome
Azathioprine	Antimetabolite agent, inhibitor of nucleotide synthesis, division and proliferation of inflammatory cells	Oral (tablets)	1–3 mg/kg/day	Cough, anorexia, nausea, vomiting, dyspepsia, hepatotoxicity, rash, blurred vision

im.: Intramuscular; iv.: Intravenous; sc.: Subcutaneous.

uveitis activity through a downregulation of $CD4^{-}CD69^{+}$ T cells in the peripheral blood [34]. MMF is effective in arresting ocular inflammation or reducing the number of relapses in patients with anterior, intermediate or posterior uveitis, refractory to other immunosuppressive agents [35,36]. However, although these findings are promising, comparative studies on larger series with longer follow-up are needed in order to confirm MMF efficacy in achieving persisting good outcomes. In a recent retrospective study, 17 children with uveitis, most intermediate, and four JIA-related, were examined. After a mean follow-up of 3 years (range 2–5 years), a steroid-sparing effect was achieved in 88% of the patients, 24% remained relapse-free and in all except one a reduction in the relapse rate was observed. Visual acuity was increased or maintained in 76%. Mild side effects (headache, rash, gastrointestinal discomfort) occurred in 41% of the patients [37]. The same rate of side effects was reported in other studies [38,39]. MMF seems to be effective in controlling inflammation after MTX failure or intolerance; however, patients with scleritis and JIA-associated CAU may have a lower chance of success [40].

Not enough data are provided to support the use of other immunosuppressive agents, such as rapamycin (sirolimus) [41], tacrolimus [42] or leflunomide [43], in JIA-related uveitis.

Biological agents

The introduction of anti-TNF agents has significantly changed the management of many autoimmune and rheumatic conditions. These agents are produced by recombinant genetic techniques and consist of chimeric or humanized monoclonal antibodies and soluble cytokine receptors. While they are effective in open-label studies, no controlled trials, regarding their use in CAU have been reported so far. We have summarized in Table 3 the main reported effects of the biological agents utilized in the treatment of CAU so far.

Etanercept

Etanercept (ETC) has been recognized as effective and safe for the treatment of polyarticular, MTX-resistant JIA [44]. This has prompted testing its efficacy for drug-refractory CAU. In a small series of JIA patients with CAU, treatment with ETC, in combination with one or two immunosuppressive drugs (MTX and/or CyA), has controlled relapses of uveitis for a medium time span of 13 months (range: 5–24 months). Significant improvement of the anterior chamber cell density was observed in 63% of eyes and visual acuity improved in 40% [45]. Rebound of inflammation occurred in some patients who discontinued therapy.

Unfortunately, several more recent reports have correlated the use of ETC with the reactivation of uveitis in the quiescent phase [46,47].

A survey among pediatric rheumatologists, including 229 children with JIA treated with ETC, reported a 8.3% uveitis relapse rate and new onset of CAU in 1% [47]. Indeed, no difference in the uveitis flare rate/year and severity were observed before and during treatment. In a recent registry-based study, the frequency of uveitis in patients on ETC treatment, compared with the expected ratio among the total number of patients treated worldwide, was significantly higher than with infliximab (IFX) ($p < 0.001$; odds ratio: 5.375) and adalimumab (ADM; $p < 0.01$; odds ratio: 8.6). Similarly, a lower improvement in the frequency of uveitis flares after ETC treatment than after IFX has been reported in adult patients with spondyloarthropathies [48]. In another small series of patients, six of whom had JIA-related uveitis, response to ETC treatment was poor in 45% of children, with more ocular complications than IFX [49].

In the only double-blind, placebo-controlled study comparing ETC (0.4 mg/kg) with placebo twice weekly for 6 months, no significant difference in the anterior segment inflammation reduction between the two groups was reported [50].

Another prospective study compared IFX and ETC in JIA-associated CAU [51]. In patients on ETC, inflammatory activity improved less and the number of uveitis flares per year was higher. Indeed, new-onset uveitis was noted in four of 24 patients (16.7%) on ETC.

Infliximab

Preliminary results on the efficacy of IFX in two small series of patients appeared promising [52,53]. The only prospective, open-label, Phase II clinical trial in adult patients showed IFX efficacy in most of the patients, but the rate of serious side effects was unexpectedly high (6/23 patients; 26%) [54]. More recently, a retrospective study reported that IFX was superior to ETC in 12 out of 21 children with JIA-related CAU, refractory to at least one standard immunosuppressive drug [55]. Indeed, a lower rate of complications, such as new-onset or worsening glaucoma or cataract, was noted. Another study, including six patients with aggressive, refractory joint and ocular disease treated for a mean of 9.5 months with IFX, reported remission of ocular inflammation in three patients, improvement in two and gain in vision in four [56]. The efficacy of anti-TNF agents (ETC, IFX and ADM) in patients with JIA-related refractory uveitis has also been investigated in a multicenter survey including 47 patients, with a mean disease duration of 45 months [57]. The overall efficacy, rated according to a composite index, was significantly higher in the IFX than in the ETC group; four patients treated with ADM all showed a good response. Another recent study reported the efficacy of IFX in 13 out of 15 children with CAU over a median treatment period of 10 weeks. Unfortunately, at a mean follow-up of 13 months (range: 12–23), CAU flared in all responders, and this was correlated to the length of treatment, confirming that IFX efficacy seems to wane over time [58].

In severe, long-standing uveitis, functional visual changes are not always related to the reduced efficacy of immunosuppressive treatment, but also to treatment-related side effects, such as optic neuritis, as reported in a few children during treatment with anti-TNF-α agents [59].

Adalimumab

Adalimumab is a fully human IgG1 monoclonal antibody that binds with high affinity and specificity to TNF blocking its interaction with the p55 and p75 cell surface TNF receptors. Vazquez-Cobian reported that ADM reduced inflammation in 21 out of 26 eyes (80.8%) of 14 children with either idiopathic or JIA-related uveitis, without significant adverse effects [60].

In a retrospective study of 18 patients with long-standing refractory uveitis, mostly JIA-related, ADM was found to be well tolerated and effective in patients previously unresponsive

Table 2. Anti-TNF agents: main properties and side effects.

Agent	Structure	Route of administration	Dose range	Side effects
Etanercept	Soluble p75 TNF receptor fusion protein	sc. injections	0.4 mg/kg twice/week, (max 25 mg/dose)	Injection site reactions, infections
Infliximab	Chimeric murine–human anti-TNF-α monoclonal antibody	iv. infusions	3–5 mg/kg at 0, 2, 6 week, then every 6–8 weeks	Infusion reactions, infections, TB reactivation, ANA and anti-DNA autoantibodies development
Adalimumab	Recombinant human IgG1 monoclonal antibody	sc. injections	20–40 mg/m^2 every other week	Injection site reactions, infections

iv.: Intravenous; sc.: Subcutaneous.

to combined therapies including IFX. The efficacy was as much as 88% for uveitis and 62% for arthritis [61].

In a recent review, Mansour summarized the differences between the three biologic agents (ETC, IFX and ADM) as far as visual results, side effects, economic impact on health and preliminary evidence of a potential superiority in JIA uveitis [62]. ADM resulted effective in controlling 80.8% of pediatric uveitis cases, with a good response observed within 2–6 weeks of therapy.

In a retrospective chart review performed on pediatric patients with chronic refractory ocular inflammation, treated with a biological response modifier (BRM) ADM, IFX and daclizumab, for a mean of 16.9 months, ADM, which was used in only five out of 23 patients, was the least effective [63]. Tynjala recently reported on a retrospective observational study of 20 JIA patients with CAU for more than 2 years, nonresponsive and/or noncompliant to topical therapy and second-line agents [64]. On ADM treatment for at least 3 months, uveitis improved in 35% of the patients. Those with better outcome were younger, had shorter JIA duration and a reduced number of active joints at the baseline. In this study, ophthalmological outcome did not seem to be as favorable as in other retrospective series [63]. Differences in patient characteristics, including age at onset of arthritis and uveitis, and response criteria definition, may explain the different rates of favorable outcome in published reports. In a prospective, nonrandomized, clinical trial, 19 patients (adults and children) received ADM for 1 year [65]. Visual acuity improved in 12 out of 38 eyes (31%), and worsened in only one (2.6%). All patients had active intraocular inflammation at baseline, and 63% achieved control of inflammation with ADM at the end of follow-up. CME, detected at optical coherence tomography (OCT) in 86% of the eyes at baseline, completely resolved in 54.5%. All patients were able to reduce at least 50% of the concomitant immunosuppressive drug dose. Nevertheless, 42% of the patients had relapses during the first year of follow-up and were treated with periocular steroid injections.

Rituximab

Rituximab (RXM) is a monoclonal antibody that reacts with CD20 receptors, inhibiting B-cell activity. A successful treatment of refractory polyarticular JIA with RXM [66] has opened a new opportunity to also treat JIA-related uveitis.

The only application of RXM in uveitis refers to an adult patient with refractory uveitis and low vision, secondary to cataract and CME. After treatment with RXM, vision and CME improved, and uveitis was stable for as long as 12 months [67].

The rationale for the potential use of RXM in CAU comes from a pathology study performed in an enucleated eye of a 12-year-old patient with JIA [68]. The immunohistochemical analysis showed that uveitis is a primarily B-cell-driven process, with few CD68- and CD8-positive suppressant cells. On this basis, B cells seem to play a crucial role in JIA anterior uveitis, and drugs or biological agents targeting B cells, such as RXM, may be advocated.

Side effects & follow-up

The main side effects of the different immunosuppressive and anti-TNF agents are summarized in Tables 2 & 3. Evidence reviews have assessed the potential carcinogenic effects of immunosuppressive therapy, extrapolated from transplant, rheumatology, skin disease and inflammatory bowel disease cohorts [69,70]. Alkylating agents, such as cyclophosphamide, increase hematologic malignancy and bladder cancer risk. Calcineurin inhibitors and azathioprine probably do not increase the overall cancer risk. TNF inhibitors may accelerate the onset of cancer in the first 6–12 months of treatment, but probably do not increase the long-term cancer risk. Changes in risk with MTX and mycophenolate mofetil appear negligible, although nontransplant data are limited for the latter agents. Immunosuppression in general may increase skin cancer risk in a sun exposure-dependent manner. In general, a brief course of alkylating agent treatment seems justifiable for severe, vision-threatening disease. Antimetabolites, TNF inhibitors and calcineurin inhibitors probably do not increase cancer risk to a degree that outweighs the expected benefits of therapy.

During treatment, we recommend performing some laboratory tests to monitor internal organ function and possible autoimmune events. The laboratory work-up should include: white blood cell count, hemoglobin, platelet count, protein profile, erythrocyte sedimentation rate, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, creatinine, blood urea nitrogen, urine analysis, antinuclear antibody, antiextractable nuclear antigens (ENA) and anti-dsDNA antibodies. These tests should be checked at the initiation of treatment and every 3 months during

Table 3. Anti-TNF agents for the treatment of JIA-related uveitis (2005–2008).

Author	Year	Study design	Anti-TNF	Regimen (patients n)	n children	Mean F/U (months)	Effectiveness				Side effects
							Reduced ocular inflammation	*Visual acuity improvement*	*Reduced local and systemic steroid dose*	*Reduced flares/ year before and after treatment*	
Richards *et al.* [52]	2005	RCR	IFX	5–10 mg/kg administered at weeks 0, 2 and 4, and thereafter 6–8 weekly	6	24	100%		100%		None
Smith *et al.* [50]	2005	RCT	ETC	ETC (0.4 mg/kg) or placebo sc. twice weekly for 6 months, followed by open-label ETC for 6 months	12	12	ETC = 43% Placebo = 40% (p = 1.00) (Reduction of AC cels to 0 or trace with topical corticosteroid < 3 times/ day - 50% reduction in N or dose of other antinflammatory drugs without inflammation increase)				Minor infections comparable in each group
Rajaraman *et al.* [53]	2006	RCR	IFX	5–10 mg/kg at weeks 0, 2, 4, and thereafter 6–8 weekly	3	12	83%				Vitreous hemorrhage, upper respiratory reaction
Saurenmann *et al.* [55]	2006	MRCR	ETC–IFX	ETC: 0.4–0.5 mg/ kg twice weekly sc. IFX: 3-10 mg/kg at weeks 0, 2, 6, then every 4–8 weeks	12	18		Not according to the underlyng disease: ETC: 54% IFX: 92%			ETC: cellulitis of the forearm
Sharma *et al.* [56]	2006	RCR	IFX	(not reported dose) infusions at 0, 2, 6, 8 weeks	6	9			50%		None
Vazquez-Cobian *et al.* [60]	2006	RCR	ADM	40 mg/m^2/week, maximum dose of 40 mg/week	9	20.7	80%				Pain at the injection site, increased i.o.p.
Foeldvari *et al.* [57]	2007	MS	ETC, IFX, ADM	ETC (34): 0.34–1.4 mg/kg; IFX (25): 4–6 mg/kg; ADM (3)	47	ETC: 21 IFX:13 ADM: 8			≥50% reduction in glucocorticoid need ETC: 65%; IFX: 92%; ADM: 100%		ETC: cutaneous hyperalgesia; IFX: anaphylactic reaction

ADM: Adalimumab; CME: Cystoid macular edema; ETC: Etanercept; IFX: Infliximab; iv.: Intravenously; MDC: Multicenter data collection; MRCR: Multicenter retrospective case review; MS: Multicenter survey; RCR: Retrospective case review; RCT: Randomized controlled trial; sc.: Subcutaneously.

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							Reduced ocular inflammation	*Visual acuity improvement*	*Reduced local and systemic steroid dose*	*Reduced flares/ year before and after treatment*	
Biester *et al.* [61]	2007	RCR	ADM	20–40 mg, every 2 weeks, when ineffective, every week	17	16.4				88.8%	Mild local reaction, burning sensations; pain around the injection site
Gallagher *et al.* [63]	2007	RCR	ADM, IFX	ADM: 40 mg/m^2 every other week; IFX: infusions (100–700 mg) at 2-week and then at 4–8 weeks	17	14	ADM (4): 100% IFX (13): 69%;	ADM (4): 50% IFX (13): 46%			IFX: elevated liver function enzymes, nausea, transient leucopenia
Tynjala *et al.* [51]	2007	MRCR	ETC, IFX	ETC: 0.4 mg/kg twice weekly sc. IFX: 3–6 mg/kg iv. at 2, 4 and 6-week intervals, later every 4–8 weeks	45	24	ETC (24): 21% IFX (21): 43%	ETC (24): 21% IFX (21): 43%			ETC: pneumonia, infection, CME, retinal ablation. IFX: peritonsillar abscess, pansinuitis and alopecia
Tynjala *et al.* [64]	2008	RCR	ADM	sc. every 2 weeks (40 mg to 18/20 patients and 20 mg to two patients weighting <30 kg)	20	18.7	35%				IFX: elevated liver function enzymes, nausea, transient leucopenia

ADM: Adalimumab; CME: Cystoid macular edema; ETC: Etanercept; IFX: Infliximab; iv.: Intravenously; MDC: Multicenter data collection; MRCR: Multicenter retrospective case review; MS: Multicenter survey; RCR: Retrospective case review; RCT: Randomized controlled trial; sc.: Subcutaneously.

the follow-up. For patients on TNF inhibitors, Mantoux tests or, alternatively, Quantiferon® TB Gold tests are recommended before the initiation of the treatment and annually during the follow-up.

Conclusion

The large variety of drugs proposed for the treatment of JIA-related uveitis reflect the lack of consensus among experts in this context. Current therapies vary considerably in type and timing and, frequently, do not adequately control eye inflammation. As a result, side effects and poor visual outcome are still quite common [71–76]. Treatment variability coupled with the timing in the use of more potent therapies are crucial issues in JIA-associated uveitis and may reflect the different outcomes reported.

According to the data from the recent literature and to our personal experience in Padua with more than 150 pediatric patients with JIA-related CAU, we suggest a practical therapeutical approach (Figure 3). It represents a sort of 'step-up treatment' in which topical drugs are progressively associated with classic systemic immunosuppressors and then, according with the disease severity, with the more recent biological agents. The better knowledge of the pathogenesis of eye inflammation and the possibility of an early prediction of the disease course will probably change this algorithm and reverse the process towards a step-down approach.

Future perspective

In order to establish indications and define appropriate systemic therapy for JIA-related CAU, controlled and randomized studies are needed for a reliable comparison of the efficacy and safety of various therapeutic agents. However, since only a small number of children are followed at each center, multicenter, multinational studies are recommended. These are also difficult because in children, CAU is rare, its course often runs into decades and many patients are concurrently treated for extraocular autoimmune disease [7]. Indeed, the lack of standardized outcome measures for disease activity and severity has consistently limited multicenter research projects. The more recent attempt to standardize ocular assessment by the SUN Working Group [77] is a major advance in this regard.

In young children with early onset uveitis the cooperation at slit lamp exam is limited, therefore, the detection of anterior chamber flares could be technically difficult. Less invasive and more recent diagnostic tools, such as OCT [78] and laser flare-cell photometry [79], will facilitate the diagnostic approach and improve the standard of care for many patients.

The management of JIA-related CAU has improved in the last decades and morbidity due to the disease is significantly decreased. In particular, the use of more effective drugs and their combination has changed the course of the disease in many patients.

The increasing knowledge of the inflammation mechanisms has led to the development of new agents that target specific cytokines interfering with the inflammatory cascade. In particular, anti-TNF agents appear effective, although their safety should be constantly monitored. Other agents, such as anti-CD20 or anti-costimulatory molecules (abatacept) [80], might represent future therapeutic options.

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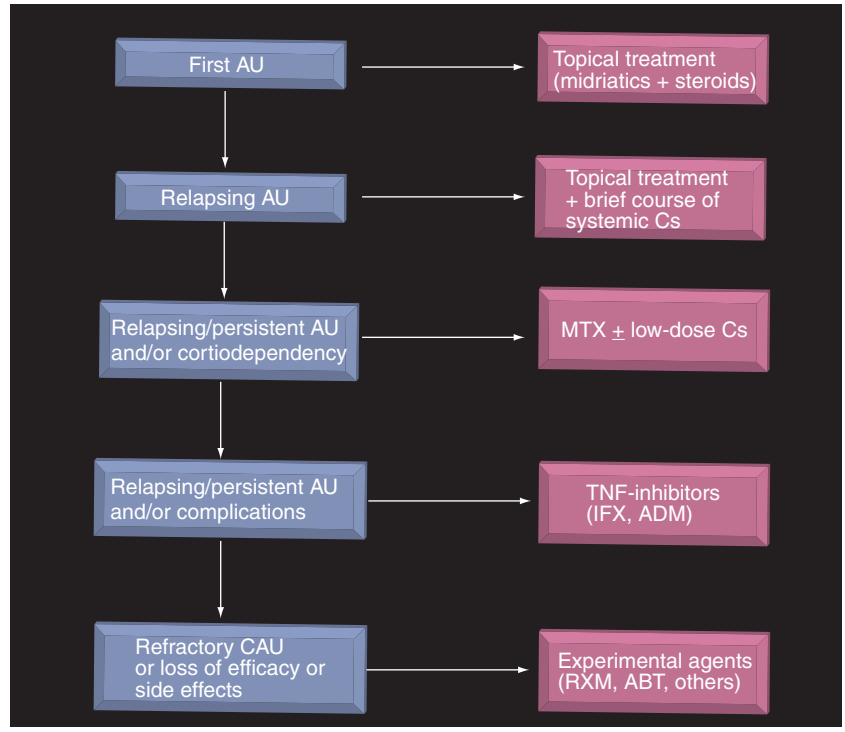

Figure 3. Algorithm of current treatment for juvenile idiopathic arthritis-related uveitis.
ABT: Abatacept; ADM: Adalimumab; AU: Anterior uveitis; CAU: Chronic anterior uveitis; Cs: Corticosteroids; IFX: Infliximab; MTX: Methotrexate; RXM: Rituximab.

Executive summary

- Chronic anterior uveitis (CAU) is the most important extra-articular complication in juvenile idiopathic arthritis (JIA), more frequent in the early onset forms, with a higher prevalence in oligoarticular (40%) than in other JIA subtypes (5–14%).
- The risk for severe visual impairment is still high owing to the development of sight-threatening complications (synechiae, band keratopathy, cataract, glaucoma and cystoid macular edema).
- Treatment is not standardized and involves a complex decision-making process, tailored by pediatric ophthalmologists and rheumatologists working in a cooperative team.
- Topical therapy alone is often inadequate to control ocular inflammation and bulbar injections are invasive and not easy to perform in children. Steroid-sparing immunosuppressive treatment is often advocated.
- Uveitis improvement with low-dose methotrexate (MTX; suggested oral dose: 7.5–15 mg/m^2/week) ranges from 45 to 72.6%, depending on the definition of inflammation and length of follow-up; no controlled studies comparing effects of early to late MTX treatment have been reported.
- To date, ciclosporin A (suggested oral dose: 3–5 mg/kg/day) has not shown clear-cut benefits as a second-line immunosuppressive drug, as monotherapy or in association with MTX.
- Mophetyl-micophenolate (suggested oral dose: 0.5–1 g/m^2/day) seems to be effective in controlling inflammation after MTX failure or intolerance. Its efficacy seems to be more relevant in intermediate or posterior uveitis, lower in JIA uveitis and scleritis.
- Evidence for anti-TNF-α effectiveness in open-label studies but not wide controlled trials, has been reported so far.
- Although initial good results for the use of etanercept (ETC; suggested twice-weekly dose: 0.4–0.5 mg/kg subcutaneously) on uveitis have been reported, several studies have correlated ETC with new-onset and/or relapsed uveitis.
- Although infliximab (IFX; suggested intravenous dose: 5–10 mg/kg at weeks 0, 2, 4, and thereafter every 6–8 weeks) seems to be superior to ETC in controlling CAU, serious side effects are frequently reported and its efficacy has been demonstrated to decrease after the first year of treatment.
- Adalimumab (suggested dose: 20–40 mg/m^2/other week subcutaneously), is as effective as IFX but is easier to administer and has better drug tolerance.

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