Recent advances in the treatment of juvenile idiopathic arthritis–associated uveitis

Judy L. Chen, Parinaz Abiri and Edmund Tsui

Abstract: Juvenile idiopathic arthritis–associated uveitis has an estimated prevalence of 10–20% in patients with juvenile idiopathic arthritis, making it the most common cause of chronic anterior uveitis in children. Prompt treatment is important to prevent development of ocular complications and permanent vision loss. In this review, we will discuss the use of immunosuppression in treatment of juvenile idiopathic arthritis–associated uveitis. This will include the use of conventional immunosuppressants, such as methotrexate, biologic anti-tumor necrosis factor agents, such as adalimumab, as well as other anti-tumor necrosis factor agents, including infliximab and golimumab. In addition, we will discuss medications currently in clinical trials or under consideration for juvenile idiopathic arthritis–associated uveitis, including interleukin-6 inhibitors (tocilizumab) and Janus kinase inhibitors (tofacitinib, baricitinib).

Keywords: IL-6 inhibitor, immunomodulatory therapy, immunosuppression, JAK inhibitor, juvenile idiopathic arthritis, TNF inhibitor, uveitis

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic and arthritic disease of childhood, with disease incidence demonstrated to be 1–22 in 100,000 and disease prevalence approximately 7–150 in 100,000.1–3 JIA is associated with a wide variety of sequelae, including skin and nail manifestations, lymphadenopathy, hepatomegaly, splenomegaly, serositis, and uveitis.4 The International League of Associations for Rheumatology (ILAR) has thus classified JIA into seven subtypes based on symptomatic presentation. Among these subtypes, JIA-associated uveitis is the most common extra-articular manifestation, often occurring in oligoarticular JIA and enthesitis-related arthritis (ERA), and less commonly in polyarticular, systemic, and psoriatic JIA.4–6

Overall, in all forms of JIA, the prevalence of uveitis ranges from 11% to 30%.7–11 The oligoarticular subtype of JIA is most common across age, gender, and ethnicity, representing 27–56% of the patient population.12 It is also associated with the highest rates of JIA-associated uveitis, which occurs in approximately 30% of diagnosed patients.13,14 ERA is slightly less prevalent, accounting for 10–20% of JIA with incidence ranging from 7% to 30%.5,15,16 The peak age of onset for JIA occurs at around 2 years, and JIA-associated uveitis presents at a median age of 3.5 years in females and 5.7 years in males.5,10 In the majority of these cases, uveitis presents within 3 years of the diagnosis of JIA, with about 50% of cases occurring during or immediately after symptomatic arthritis. In about 10% of patients, uveitis presents before the onset of arthritis.6,7,12,17,18

Uveitis, in accordance with the Standardization of Uveitis Nomenclature (SUN) international working group, is classified via anatomical location and time course of the disease.19 While uveitis may present as anterior, intermediate, posterior, or panuveitis, JIA classically causes an anterior uveitis and rarely presents as panuveitis.5,6,7,19 JIA-associated uveitis is also typically a chronic disease, in which patients can have persistent inflammation with relapse within 3 months of discontinuing treatment. In contrast, acute disease is characterized by sudden onset and limited duration of symptoms.

Therapeutic Advances in Ophthalmology

Review

Ther Adv Ophthalmol
2021, Vol. 13: 1–14
DOI: 10.1177/2515841420984572
© The Author(s), 2021. Article reuse guidelines: sagepub.com/journals-permissions

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
and is classified as recurrent if relapses occur after at least 3 months of inactivity of treatment.19

Studies have shown that different subtypes of JIA are each associated with different presentations of uveitis. For instance, chronic anterior uveitis has the highest rate of occurrence in oligoarticular and rheumatoid factor-negative polyarticular JIA and occurs most commonly overall at a rate of 68.3%.4,6,7 In contrast, acute anterior uveitis and recurrent anterior uveitis are often associated with ERA.4,6 These collectively occur in 28.2% of patients, with 16.2% presenting with acute anterior disease and 12% acquiring recurrent anterior disease.7 Panuveitis generally occurs at a much lower rate of 3.5%, and no evidence has demonstrated its association with a specific JIA subtype.7

Various studies have been performed to identify the role of gender and ethnicity in the incidence of JIA-associated uveitis. While variations in gender distribution are noted in different population studies, the incidence of JIA in females is consistently significantly higher than in males, with presentation likely to occur at a younger age.5,20 Ethnic studies have suggested a significantly greater prevalence in those of European descent, followed by individuals from Latin America, Africa, Middle East, and Asia.21,22

Several clinical and genetic risk factors have been identified for the development of JIA-associated uveitis, with the most significant being younger age at the onset of JIA symptoms.8,20,23–25 The risk for uveitis based on JIA subtype has been controversial with conflicting studies demonstrating higher risk with oligoarticular JIA as opposed to subtype independence.8,20,23 Inconsistencies in the significance of antinuclear antibodies (ANA) positivity have also been noted, with the majority of studies demonstrating its impact in females alone.8,20,23–25 Specifically, ANA-positive females have been shown to have higher risk for the development of chronic anterior uveitis.6,12,26,27 Female JIA patients have also demonstrated higher susceptibility to uveitis when they possess a specific amino acid motif in HLA-DRβ1.28 In contrast, patients positive for HLA-B27 have been shown to have a higher risk for developing acute anterior uveitis, more commonly males with the ERA subtype.3,6,26,27 Finally, additional studies have demonstrated increased risk for developing uveitis in the setting of elevated erythrocyte sedimentation rate (ESR) at the time of JIA diagnosis and arthritis.29,30

Pathophysiology
The pathophysiology of JIA and JIA-associated uveitis remains unclear, but is likely an autoimmune phenomenon resulting from interaction between genetic and environmental factors, including infection, stress, and trauma.4 Genetic predisposition is supported by reports of familial cases and associations with certain HLA genes and specific genetic markers as discussed in the previous section.28,31,32 Evidence for an autoimmune etiology is provided by histological specimens of eye biopsies demonstrating the involvement of both B- and T-lymphocytes as well as effectors of the innate immune system, such as macrophages.33,34 High concentrations of proinflammatory cytokines and chemokines have also been found in the aqueous humor of eyes with JIA-associated uveitis, including interleukin (IL)-2, IL-6, IL-13, IL-18, interferon (IFN)-γ, tumor necrosis factor (TNF), CD54, CCL5, and CXCL10.35 Finally, ANA associations suggest the role of auto-antibodies in the pathogenesis of uveitis in JIA patients.

Clinical presentation
The presentation of uveitis can vary among JIA patients but is most commonly a chronic anterior uveitis, which can be asymptomatic. This is in contrast to the acute and recurrent forms, which usually present with headaches, eye pain, redness, photophobia, and visual changes, but JIA patients may have difficulty in reliably describing their symptoms if they present at an early age.4,6,19 Both symptomatic and asymptomatic disease can be vision threatening, making ocular screening vital in JIA-diagnosed children.

While most cases of JIA-associated uveitis occur after the onset of arthritis, a small subset (10%) may have uveitis as the first presenting sign of underlying disease.5 Pediatric patients presenting with ocular inflammation should therefore be screened for systemic symptoms, such as fever, fatigue, generalized aches, changes in appetite, and rash.4,19

Diagnosis
Early diagnosis is essential in uveitis to prevent serious vision-threatening complications, especially in
the young JIA patient population. Studies have demonstrated a complication rate between 37% and 70% at the initial ophthalmologic examination, indicated by the presence of band keratopathy, posterior synechiae, cataracts, glaucoma, hypotony, macular edema, epiretinal membrane, and optic disk swelling.\textsuperscript{17,25,36,37} The rate of complications is higher in patients with chronic anterior uveitis, likely a result of delayed diagnosis due to asymptomatic disease.\textsuperscript{6,19}

Screening for uveitis is performed with a complete eye examination, encompassing anterior slit lamp and dilated fundus examination, visual acuity testing, and measurement of intraocular pressure.\textsuperscript{6,19} Specific information that should be documented includes the grading of cells in the anterior chamber (AC), AC flare, vitreous cells, and vitreous haze or debris, which can then be utilized to monitor patients over their disease course and guide treatment.\textsuperscript{5,19,29} Visually significant cataracts and glaucoma are important comorbidities in JIA patients, and it is therefore vital to also closely assess their visual acuity, intraocular pressure, lenticular changes, and degree of disk cupping.\textsuperscript{19}

**Surgical therapies**

Uveitic complications can be visually disabling and may require surgical intervention for visual rehabilitation or prevention of further vision loss. Studies have shown that among patients with JIA-associated uveitis, an estimated 51% of develop synechiae, 34% develop band keratopathy, 20% develop cataracts, and 17% develop glaucoma.\textsuperscript{18,38,39} If surgical treatment is deemed necessary, age-appropriate standard of care practice is followed, and it is recommended that surgery is performed after at least 3 months of inflammatory quiescence to optimize outcomes.

**Current treatment guidelines**

In 2019, the American College of Rheumatology published guidelines on the medical management of JIA-associated uveitis based on existing evidence and consensus of an expert panel of pediatric rheumatologists and uveitis specialists. Medications assessed in the guideline included topical and systemic glucocorticoids, nonbiologic disease-modifying anti-rheumatic drugs (DMARDs; methotrexate, leflunomide, mycophenolate, and cyclosporine), and biologic DMARDs (TNF inhibitors adalimumab, infliximab, etanercept; CTLA-4 inhibitor abatacept; and IL-6 inhibitor tocilizumab).

Per these guidelines, patients with active JIA-associated chronic anterior uveitis are recommended to be initially started on prednisolone acetate 1% topical eye drops. This is preferred over difluprednate 0.05% topical drops and systemic glucocorticoids. Furthermore, it is recommended to increase topical glucocorticoids for short-term control as opposed to adding systemic glucocorticoids. If 1–2 drops per day are needed to maintain control for 3 months or longer, initiation of systemic immunomodulatory therapy is recommended to allow for the tapering of drops. If patients continue to require 1–2 drops per day for uveitis control despite systemic therapy for 3 months or longer, then changing or escalating systemic therapy is recommended over maintaining current therapy. If control is maintained, topical steroids should be first tapered before systemic therapy. There should be at least 2 years of quiescence before beginning to taper systemic therapy.\textsuperscript{40}

In the selection of systemic therapy, methotrexate is the initial treatment of choice, with subcutaneous delivery preferred over oral medication. If uveitis is severe with sight-threatening complications, monoclonal antibody TNF inhibitors (adalimumab or infliximab) are preferred to nonmonoclonal antibody TNF inhibitor etanercept as a supplement to methotrexate. If uveitis persists, increasing the dosage and frequency to above-standard levels are recommended before switching to another agent. However, if a change is necessary due to a lack of response, switching to another monoclonal antibody TNF inhibitor is recommended over changing to an agent in another category. If active uveitis is refractory to methotrexate and two monoclonal antibody TNF inhibitors, alternative options for nonbiologic DMARDs include mycophenolate, leflunomide, and cyclosporine, and for biologic DMARDs include abatacept or tocilizumab.\textsuperscript{40}

Finally, for acute anterior uveitis occurring in patients already on systemic therapy for JIA spondyloarthritis, it is recommended that they continue their existing regimen and add topical glucocorticoids as the first step due to the short duration of these episodes.\textsuperscript{40}
**Recent advances in treatment**

As detailed in the prior section, systemic immunosuppression with DMARDs is typically necessary to achieve disease-free remission in patients with juvenile spondyloarthropathies and associated chronic uveitis. Several randomized controlled trials have been performed in the last decade that guide the current standard of care. The following section summarizes these trials and details the growing evidence for alternative classes of immunomodulatory therapy (IMT) for treatment of JIA-associated uveitis (see Table 1 for a summary of the treatment options and evidence discussed).

**Conventional immunosuppression**

Antimetabolites are the standard class of conventional immunosuppressive agents used for initial treatment of JIA uveitis. Classically, patients are started on methotrexate, but azathioprine, leflunomide, and mycophenolate mofetil have been used to a lesser degree in cases of refractory or resistant disease. T-cell inhibitors, such as cyclosporine and tacrolimus, have also been used, as well as alkylating agents, such as cyclophosphamide and chlorambucil, though the latter in a limited manner due to medication toxicity and side effects of increased malignancy risk and sterility.

Methotrexate has been found to be efficacious and well tolerated by patients for several rheumatologic conditions and is considered as first-line treatment for JIA-associated uveitis.\textsuperscript{41,42} Approximately three-quarters of patients with ocular inflammation are expected to respond to methotrexate therapy, with topical steroid-sparing effect observed after about 3–9 months of therapy.\textsuperscript{43} Children with JIA who are treated with methotrexate have been observed to develop uveitis at a lower rate than those who were not treated, suggesting that early initiation of treatment may prevent the onset of uveitis in children.\textsuperscript{44} Traditionally, methotrexate is administered as oral tablets or subcutaneous injections weekly at a dose of 7.5–12.5 mg/m\textsuperscript{2}/week. Of note, methotrexate has been studied at doses as high as 20 mg/m\textsuperscript{2}/week, and it has been demonstrated that high-dose methotrexate (\(\geq 15\) mg/m\textsuperscript{2}/week) may be associated with a shorter time to remission as compared with low-dose methotrexate, with comparable rates of steroid-sparing and adverse effects.\textsuperscript{45}

Patients with JIA uveitis as opposed to idiopathic chronic uveitis consistently demonstrate increased risk for relapse after treatment withdrawal, and timing for safe discontinuation of methotrexate in these patients following control of their disease is yet to be determined.\textsuperscript{78–80} A retrospective cohort study by Simonini and colleagues\textsuperscript{78} evaluating predictors of relapse in children with chronic uveitis found shorter time to inactivity after starting systemic therapy, namely within 6 months of initiation, was associated with higher probability of maintaining remission. Of note, among those who achieved inactivity within 6 months, children on anti-TNF agents had greater probability of maintaining remission than those on methotrexate.\textsuperscript{78} Generally, at least 2 years of inactivity are recommended prior to attempting to taper systemic immunomodulatory therapy.\textsuperscript{40} Relapse-free survival after withdrawal of methotrexate has been demonstrated to be significantly longer in JIA patients who have been treated with methotrexate for more than 3 years, children who are older than 8 years at the time of withdrawal, and patients who have had inactivity of uveitis of longer than 2 years before withdrawing methotrexate.\textsuperscript{81} Furthermore, a 1-year increase in duration of inactive uveitis before the withdrawal of methotrexate results in a decrease in hazard for new relapse of 93%.\textsuperscript{81}

The remaining antimetabolites appear to be inferior to methotrexate for uveitis control in JIA. Azathioprine may have limited utility either as monotherapy or in combination with other immunosuppressive drugs. A retrospective multicenter study demonstrated that during a mean follow-up period of 26 months, 61.5% of patients achieved inactivity on azathioprine monotherapy, and 66.7% of those who used azathioprine in combination with other immunosuppressive drugs; azathioprine was found to reduce the required dosages of systemic immunosuppression and topical and systemic steroids.\textsuperscript{46} Cyclosporine has been less successful, with a multicenter study by Tappeiner and colleagues\textsuperscript{47} reporting inactivity was attained in only 24% of patients on monotherapy, and 48.6% of patients on combination therapy, with no resolution of pre-existing cystoid macular edema achieved. In a single published study regarding patients with JIA uveitis, leflunomide was associated with a higher rate of uveitis flares and requirement of additional TNF-inhibitor therapy as compared with methotrexate.\textsuperscript{48} Similarly, odds of inflammation control with mycophenolate mofetil appear to be lower for patients with JIA-associated uveitis refractory to methotrexate than other etiologies.\textsuperscript{49} Overall, these observations suggest that...
| Drug               | Mechanism of action                      | Administration and dosage                                                                 | Approved indications                                                                 | Adverse effects                                                                 | References | Ongoing trials (ClinicalTrials.gov identifier) |
|--------------------|-----------------------------------------|--------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------|-----------------------------------------------|
| Methotrexate       | Dihydrofolate reductase inhibitor        | Oral or subcutaneous injections (7.5–25 mg weekly)                                          | Psoriasis, rheumatoid arthritis, juvenile idiopathic arthritis                    | Nausea, fatigue, liver toxicity, cytopenias                                   | 41–45      | –                                             |
| Azathioprine       | Purine nucleoside analog                | Oral [1.0–2.5 mg/kg daily, up to 150 mg daily]                                               | Rheumatoid arthritis, prevention of renal transplant rejection                   | Nausea, liver toxicity, bone marrow suppression                                | 46         | –                                             |
| Cyclosporine       | Calcineurin inhibitor                   | Oral [2.5–5.0 mg/kg daily]                                                                  | Rheumatoid arthritis, psoriasis, refractory posterior uveitis, Behçet disease, prevention of organ transplant rejection | Nephrotoxicity, hypertension, anemia, gingival hyperplasia, hirsutism, muscle cramps, neurological symptoms (paresthesias, tremors, headache) | 47         | –                                             |
| Leflunomide        | Dihydro-orotate dehydrogenase inhibitor | Oral [10–20 mg daily]                                                                       | Rheumatoid arthritis, psoriatic arthritis                                        | Diarrhea, nausea, liver toxicity, hypertension, cytopenias                     | 48         | –                                             |
| Mycophenolate mofetil | Inosine monophosphate dehydrogenase inhibitor | Oral [2–3 g daily]                                                                           | Prevention of organ transplant rejection                                           | Diarrhea, liver toxicity, cytopenias, opportunital infections                  | 49         | –                                             |
| Chlorambucil       | Alkylating agent                        | Intravenous [0.1–0.2 mg/kg daily for 3–6 weeks, titrated to suppress white blood cell count between 2800 and 3000/mm³] | Chronic lymphocytic leukemia, malignant lymphomas                                 | Bone marrow suppression, secondary malignancy (bladder cancer), sterility       | 50         | –                                             |
| Adalimumab         | TNF-α inhibitor [(fully humanized monoclonal antibody)] | Subcutaneous injection [80 mg loading dose, followed by 40 mg on day 8 and every 1–2 weeks thereafter] | Noninfectious intermediate, posterior and panuveitis; juvenile idiopathic arthritis, rheumatoid arthritis, plaque psoriasis, ankylosing spondylitis, Crohn’s disease | Opportunistic and invasive fungal infections, reactivation of underlying hepatitis and tuberculosis, malignancies (lymphomas, skin cancers), demyelinating disease, congestive heart failure, induction of autoimmunity | 51–61      | NCT03816397                                  |
| Infliximab         | TNF-α inhibitor [(chimeric mouse-human monoclonal antibody)] | Intravenous infusion [loading: 3–5 mg/kg at 0, 2, 6 weeks; maintenance: 3–10 mg/kg every 4–8 weeks, up to 20 mg/kg monthly in children] | Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn’s disease, ulcerative colitis | See section in Adalimumab                                                    | 57–59      | –                                             |
| Golimumab          | TNF-α inhibitor [(fully humanized monoclonal antibody)] | Subcutaneous injection [50 mg monthly] or intravenous infusion [loading: 2 mg/kg at weeks 0 and 4; maintenance: every 8 weeks] | Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis                | See section in Adalimumab                                                    | 62,63      | NCT04200833                                 |
| Tocilizumab        | IL-6 inhibitor [(monoclonal antibody)]   | Subcutaneous injection [162 mg every other week] or intravenous infusion [4–12 mg/kg every 4 weeks] | Rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis           | Respiratory tract infections, hypertension, liver toxicity [increased ALT]      | 64–68      | –                                             |
| Abatacept          | T-cell costimulation modulator [soluble fusion protein] | Subcutaneous injection [weekly] or intravenous infusion [10 mg/kg every 4 weeks, up to 1000 mg] | Rheumatoid arthritis, juvenile idiopathic arthritis                                | Headache, respiratory tract infections, nausea                                 | 69–72      | NCT01279956                                  |
| Tofacitinib/baricitinib | Janus kinase inhibitor                   | Oral [10 mg daily]                                                                            | Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis                     | Headache, respiratory tract infections, diarrhea                               | 73,74      | NCT04088409                                  |
| Rituximab          | CD20 inhibitor [(chimeric mouse-human monoclonal antibody)] | Intravenous infusion [for rheumatoid arthritis, two 1000 mg infusions separated by 2 weeks, every 4 months] | Non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis | Infections, infusion reaction, cytopenias, nausea, diarrhea, headache, muscle spasms, peripheral edema | 75–77      | –                                             |

IL, interleukin; TNF, tumor necrosis factor; ALT, alanine aminotransferase.
these alternative antimetabolites should be considered secondary to methotrexate and likely be used only in combination with other immunosuppressives rather than as monotherapy.

Finally, given their toxicity and extensive side-effect profile, alkylating agents are typically the last resort for refractory uveitis, but may have good efficacy in patients resistant to steroids and other immunomodulatory therapies. A case series based at the Massachusetts Eye and Ear Infirmary found that chlorambucil was a safe, effective alternative for intractable noninfectious uveitis. Out of 10 patients with JIA-associated uveitis, eight achieved control of intraocular inflammation; one initially responded but relapsed after discontinuation of chlorambucil, and one patient failed to respond.

**Biologic therapeutics**

The ‘biologics’ are large, complex molecules derived from living organisms or created by recombinant DNA technology and comprise monoclonal antibodies, soluble receptors, cytokines, and cytokine antagonists. These agents are used for patients in whom conventional immunosuppression is poorly tolerated or incompletely effective and are used as second-line treatment for patients with JIA-associated uveitis. Combination therapy with conventional immunomodulatory therapy is considered safe and may also be synergistic by reducing the development of anti-drug antibodies; a common example of this is the combination of methotrexate with infliximab.

Among the biologics, the largest body of evidence for JIA uveitis has been amassed for the TNF inhibitors and specifically the monoclonal antibodies adalimumab (Humira®, Abbvie) and infliximab (Remicade®, Janssen). Adalimumab is currently the only FDA-approved medication for use in noninfectious uveitis, and two recent randomized controlled trials, SYCAMORE and ADJUVITE, established the efficacy and safety of adalimumab in JIA uveitis patients. Etanercept, a soluble transmembrane TNF receptor, also falls within this class; while effective for juvenile arthritic disease, etanercept has been observed in several studies to not affect the frequency or severity of associated uveitis, with a significant proportion of patients suffering relapses despite etanercept therapy. Therefore, adalimumab and infliximab are both preferred over etanercept for treatment of ocular inflammatory disease.

Other classes of biologics with reported benefit in smaller case series or ongoing clinical trials that will be discussed include interleukin (IL)-6 inhibitors, T-cell costimulation modulator/inhibitors, Janus kinase (JAK) inhibitors, and CD20 inhibitors. The majority of studies for these immunomodulatory agents evaluate their efficacy in severe refractory uveitis that has failed multiple immunosuppressives, including antimetabolites and at least two TNF inhibitors. Additional high-quality comparative studies will be needed to determine the utility of these agents further upstream in the treatment algorithm for JIA uveitis.

**TNF inhibitors.** The monoclonal antibody TNF inhibitors adalimumab and infliximab have demonstrated good efficacy in preventing flares and inducing disease-free remission in patients with JIA uveitis. SYCAMORE was a multicenter randomized, placebo-controlled, double-blinded trial examining the utility of adalimumab in 90 patients with JIA-associated uveitis refractory to topical or systemic steroids and methotrexate. Addition of adalimumab to methotrexate significantly delayed the time to treatment failure, reduced the need for two or more drops of topical glucocorticoids per day, and decreased the risk of treatment failure by approximately 75% as compared with placebo over a follow-up period of 6 months. Treatment failure was observed in 27% of patients in the adalimumab group versus 60% in the placebo group, and adalimumab was overall well tolerated.

ADJUVITE was another double-blinded, randomized controlled trial evaluating the use of adalimumab for JIA-associated uveitis. Patients aged 4 years or older with ocular inflammation refractory to topical steroids and methotrexate were randomized to placebo or adalimumab 40 mg injections every other week (24 mg/m² if younger than 13 years old). Laser flare photometry measurements improved in the treatment group within 2 months of initiating therapy. Furthermore, the need for topical, local, and systemic steroids decreased in most treated patients within 2–12 months of treatment, thus demonstrating early improvement in status of ocular inflammation. Over 12 months of follow-up, adalimumab was well tolerated and associated with inactivity in the majority of patients.
Adalimumab is administered subcutaneously with a loading dose of 80 mg on day 1 and a 40 mg injection on day 8, followed by maintenance injections of 40 mg every 2 weeks. Should patients fail adalimumab on standard biweekly dosing, off-label escalation to weekly treatment may achieve control of inflammation. The first report describing success of weekly adalimumab for ocular inflammation included six JIA patients, out of which five responded within 6 months.54 Liberman and colleagues also recently published the largest series to date of patients with ocular inflammatory disease who were escalated to weekly dosing due to inadequate control, including one subject with JIA-associated uveitis. This patient regained long-term control of inflammation with topical steroid-sparing effect and did not suffer any serious side effects over 12 months of follow-up.55

As with methotrexate, the optimal duration of adalimumab therapy remains unclear at this time. Following the aforementioned SYCAMORE trial, Horton and colleagues described outcomes of the trial participants after adalimumab had been discontinued after a maximum of 18 months or after treatment failure within this time. Drug-induced remission of JIA uveitis did not persist when adalimumab was withdrawn after 1–2 years of treatment on the trial, with 92% of participants ultimately restarting therapy due to relapse.56 ADJUST is a clinical trial based out of the Proctor Foundation at University of California, San Francisco that is currently recruiting patients to provide guidance regarding stopping adalimumab in JIA; children who have been controlled on adalimumab for 12 months or more will be randomized to continuing adalimumab versus a placebo (NCT03816397).

In terms of efficacy and safety profile, several studies comparing adalimumab and infliximab suggest that adalimumab is at least comparable to infliximab, if not more favorable.57–59 A meta-analysis by Simonini and colleagues60 in 2014 reported similar efficacy between adalimumab and infliximab, but more remission was attained with use of adalimumab. Switching biologic agents can also restore control of inflammation in refractory cases of uveitis; Dhingra and colleagues61 found that three JIA patients with persistent uveitis within their series achieved disease-free remission with reduced concomitant immunosuppressive therapy when switched from infliximab to adalimumab. Moreover, adalimumab is generally favored over infliximab due to ease of administration with subcutaneous injections as opposed to infusions.

Golimumab and certolizumab have established efficacy for arthritic disease within the rheumatologic literature, and they represent future alternative TNF inhibitors for JIA-associated uveitis. Small case series suggest golimumab may be a viable therapeutic option in cases of JIA-associated uveitis refractory to other TNF inhibitors.62,63 A retrospective single-center study out of the Medical University of Graz in Austria will also be reporting on the outcomes of a series of 10 patients who were started on golimumab after failure of standard conventional immunosuppression and adalimumab over 10-year follow-up (NCT04200833).

**Interleukin-6 inhibitors.** IL-6 inhibitors are humanized monoclonal antibodies that bind to the cellular receptor for interleukin-6 and inhibit the cytokine’s proinflammatory effects. Elevated IL-6 levels have been found in JIA and correlated with the extent and severity of joint involvement, and IL-6 inhibition in animal models of uveitis reduced the risk of disease development.85,86 Tocilizumab (Actemra®, Genentech) is an IL-6 inhibitor approved for polyarticular and systemic JIA and represents another possible therapeutic option in patients with severe refractory uveitis, with studies suggesting that tocilizumab may in particular be beneficial for uveitic macular edema.

At the time of this publication, STOP-Uveitis is the sole randomized, controlled multicenter clinical trial evaluating the efficacy and tolerability of tocilizumab in patients with noninfectious uveitis. Patients were randomized into two groups and received either 4 or 8 mg/kg of intravenous tocilizumab. In both treatment groups, nearly half of patients demonstrated a two-step decrease in vitreous haze, and central macular thickness decreased significantly with a corresponding improvement in visual acuity by the end of 6 months.64

Recent case series have reported on the use of tocilizumab in JIA-associated uveitis. A study of 25 patients with severe JIA uveitis refractory to anti-TNF therapy and conventional immunosuppression found that those treated with 8 mg/kg of tocilizumab infusions every 4 weeks experienced improvement in AC cell, central macular edema, and visual acuity as quickly as 2–4 weeks after initiating therapy and sustained control over 12 months of follow-up.65 Nineteen out of 25 patients in this series achieved complete remission of uveitis.65 Tappeiner and colleagues also reported outcomes of 17 patients with disease refractory to systemic steroids, methotrexate,
and at least one TNF inhibitor who were placed on 8 mg/kg of intravenous tocilizumab. Ten out of 17 patients achieved inactivity after a mean of 5.7 months, but three of these patients suffered recurrences in follow-up. Macular edema that was present at baseline in five patients all improved with tocilizumab.

Tocilizumab can also be delivered as a subcutaneous injection, which has similar efficacy to the intravenous formulation for arthritic disease, but the data are mixed for ocular inflammation. APTITUDE was a non-randomized, interventional study examining the effects of adding subcutaneous tocilizumab to methotrexate for children with JIA uveitis refractory to both methotrexate and TNF inhibitors.67 Unfortunately, the phase II trial did not reach the primary endpoint to support proceeding with a phase III trial, but found that 7 of 21 participants in the study responded to tocilizumab treatment, suggesting subcutaneous tocilizumab may serve as a reasonable alternative for some patients with TNF inhibitor-refractory disease. In 2017, Quesada-Masachs and colleagues68 reported less favorable outcomes with subcutaneous tocilizumab; four patients with JIA-associated uveitis and sustained clinical response to intravenous tocilizumab experienced flares (three ocular, one joint) after switching to the subcutaneous form. Further investigation will need to be done to determine the comparative efficacy of subcutaneous and intravenous tocilizumab for JIA uveitis.

T-cell costimulation modulator/inhibitors. Abatacept (Orencia©, Bristol-Meyers Squibb) is a selective T-cell costimulation modulator that has been demonstrated to be a valid second-line alternative to anti-TNF agents for rheumatoid arthritis and JIA in refractory cases.87,88 The molecule binds CD80 and CD86 T-cell receptors and also inhibits a co-stimulating signal by binding the B7 (CD80) receptor found on antigen-presenting cells, to prevent stimulation of T-cells in the inflammatory cascade.89

One of the earliest studies by Zulian and colleagues in 2010 reported the use of intravenous abatacept in a series of seven patients with severe anti-TNF refractory JIA-associated uveitis. All patients had failed previous IMT, including at least two anti-TNF therapies. All patients responded to abatacept, with six out of seven maintaining clinical remission after a mean of 9.2 months of treatment, and the mean frequency of uveitis flares during the 6 months before and after treatment decreased from 3.7 to 0.7 episodes.69 Only one patient withdrew due to oral mycosis and arthritis flare; no others experienced side effects.69 A subsequent case report by Kenawy and colleagues in 2011 reported the prospective use of abatacept in two patients with JIA-associated uveitis refractory to multiple antimetabolites and TNF inhibitors. Following administration of abatacept infusions, response of AC cell and vitreous haze was noted as soon as 2 months of therapy, and disease-free remission was sustained throughout 9- to 12-month follow-up for both patients. In contrast, Tappeiner and colleagues71 observed sustained response to abatacept was uncommon in their series of 21 patients with severe refractory uveitis, with uveitis recurring in 8 of 11 patients who had achieved inactivity, and remaining active in 10 cases.

While the former studies were performed in patients who had failed multiple agents, Birolo and colleagues72 evaluated the comparable efficacy of abatacept when used as the first-line or second-line biologic agent in their series of 35 patients with severe JIA-associated uveitis. No significant difference in remission rate, decrease in frequency of uveitis flares, or ocular complications was observed between the groups on abatacept as first-line as opposed to second-line treatment. Both groups achieved remission in more than 50% of patients during the 12-month treatment period and experienced a decrease in the mean frequency of uveitis flares to 1.2 episodes post-treatment.72

Given the mixed data, further studies are needed to elucidate the effectiveness of abatacept for JIA-associated uveitis and its role within the armamentarium of immunomodulatory therapy. A clinical trial of abatacept completed for noninfectious uveitis in 2019 is pending release of results at the time of this publication (NCT01279954).

Janus Kinase inhibitors. Another class of IMT with potential applications in uveitis are the Janus kinase (JAK) inhibitors, such as tofacitinib and baricitinib, which are currently approved for treatment of rheumatoid and psoriatic arthritis.90 Janus kinases are cytoplasmic tyrosine kinases associated with cytokine membrane receptors and exert proinflammatory effects by interacting with receptors for interleukins, growth factors, and hormones. JAK2 and JAK3 inhibitors, including tofacitinib, block the activity of interleukins IL-2,
IL-4, IL-15, and IL-21 to attenuate inflammation in autoimmune disease.\textsuperscript{91,92}

A few reports have emerged describing the potential utility of JAK inhibitors for JIA-related uveitis and associated macular edema. Bauermann and colleagues described the course of a patient with JIA uveitis complicated by intolerance and failure of numerous therapies, including methotrexate, cyclosporine, mycophenolate mofetil, adalimumab, golimumab, infliximab, tocilizumab, and rituximab, who required intravitreal dexamethasone implantation for resolution of macular edema. Following initiation of oral tofacitinib in combination with methotrexate, AC inflammation resolved, with significant improvements in macular edema as well as visual acuity.\textsuperscript{73} Another recent series by Miserocchi and colleagues reported four patients with JIA and uveitis refractory to multiple immunosuppressive agents who were then placed on either baricitinib or tofacitinib. They observed greater reduction in ocular inflammatory activity than in articular disease within their cohort, and no serious systemic side effects necessitating cessation of therapy.\textsuperscript{74}

To further characterize the effects of JAK inhibitors on pediatric uveitis, an international, multicenter, open-label controlled study sponsored by Eli Lilly and Company is currently underway comparing the use of oral baricitinib versus adalimumab for patients with active JIA-associated uveitis or chronic anterior ANA-positive uveitis (NCT04088409).

\textbf{CD20 inhibitors}. Enucleated JIA-uveitis specimens have demonstrated focal aggregates of CD20\textsuperscript{+} B-cells, which may implicate a role of B-cells in the pathogenesis of JIA uveitis.\textsuperscript{93} In a handful of case series, the CD20 inhibitor rituximab (Rituxan\textsuperscript{©}, Genentech) has demonstrated the ability to achieve remission and corticosteroid- and immunosuppressive-sparing effect for some refractory cases of JIA-associated uveitis. One retrospective, multicenter study evaluated the use of rituximab for active JIA uveitis and arthritis that was refractory to topical and systemic steroids, immunosuppressives, and at least one of the TNF inhibitors.\textsuperscript{75} After one rituximab cycle with follow-up of 11 months, uveitis inactivity was achieved in 7 out of 10 patients for a mean of 7.5 months with improvement in macular edema. However, out of seven initial responders, four patients, who were all noted to have ANA+/HLA-B27\textsuperscript{−} oligoarthritis, required additional treatment for recurrence of uveitis during the follow-up period. The remaining three of the original 10 patients, who had ANA+ polyarthritis or ANA+/HLA-B27+ oligo- and polyarthritis, experienced persistent uveitis despite rituximab therapy. The authors discussed that relapses likely occurred in conjunction with the expected restoration of B-cell levels within 9–12 months following rituximab treatment and that poor response in some patients may be related to the persistence of autoreactive plasma cells that are the predominant producers of antibodies.\textsuperscript{75}

Miserocchi and colleagues\textsuperscript{76} also reported their experience with rituximab in eight patients with refractory JIA uveitis who required systemic and topical steroids and had failed conventional immunosuppression and anti-TNF inhibitors. One patient had additionally failed abatacept, and another two patients, chlorambucil. In accordance with rheumatologic protocol, patients were administered rituximab infusions on days 1 and 15, and some also received a recall third infusion at month 12. Over a mean follow-up of 11.75 months following the first rituximab infusion, seven out of the eight patients achieved complete control of uveitis and were in clinical remission, with decrease in inflammation noted 4 months after their first infusion.\textsuperscript{76} Systemic prednisolone dose decreased from an average 18.2 mg/day to 12.5 mg or less per day, and six patients reduced topical steroid drops from a mean of 3.12 to 0.75 drops/day, with two discontinuing topical therapy altogether. Concomitant immunosuppressants were discontinued on five out of six patients at the last visit. In a follow-up publication, long-term use of rituximab over a mean follow-up of 44.75 months with an average of 8.75 infusions in these patients revealed similar outcomes.\textsuperscript{77} All patients achieved remission of uveitis, though two patients discontinued treatment due to inefficacy for arthritic disease. Five patients were able to discontinue systemic corticosteroids and immunosuppressants by the end of follow-up. Neither of these studies found worsening of visual function or drug-related complications necessitating cessation of therapy.

\textbf{Conclusion and future directions}

JIA is the most prevalent rheumatologic disease among children and is commonly associated with chronic uveitis. Without adequate control of ocular inflammation, patients may develop
Therapeutic Advances in Ophthalmology 13

complications leading to permanent visual loss with significant lifelong disability. For patients who are unable to be tapered to a safe long-term dose of topical and oral steroids, the current treatment algorithm recommends initiation of treatment with methotrexate, followed by a monoclonal antibody TNF inhibitor such as adalimumab. Other biologics, including IL-6 inhibitors, T-cell costimulation modulators, JAK inhibitors, and CD20 inhibitors, that have demonstrated efficacy for arthritis may also serve as rescue options for treatment-refractory uveitis. Future avenues for investigation include IL-1 inhibition, which has shown benefits for systemic JIA, as well as analysis of ocular fluids that will lead to an improved understanding of the primary mediators of ocular inflammation in JIA patients. Interleukin-29/interferon-γ levels have been demonstrated to be reduced in patients with JIA uveitis as compared with those with idiopathic uveitis, implying that aberrant interferon-γ signaling may play a role in JIA-associated disease. Finally, PEDIAS-U is a multicenter study that is currently recruiting patients with JIA with and without uveitis; the aims of this study are to evaluate chemokines and cytokines from tear samples of patients with JIA, as well as genetic markers from saliva and serum samples, that may inform the susceptibility of JIA patients to developing uveitis. Results from these and future studies have the potential to guide prediction of patients who will develop ocular disease and may have implications for more targeted, individualized therapy for patients with JIA uveitis.

Conflict of interest statement
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by an Unrestricted Grant from Research to Prevent Blindness, Inc., to the Department of Ophthalmology at UCLA.

ORCID iDs
Parinaz Abiri https://orcid.org/0000-0002-0520-6863
Edmund Tsui https://orcid.org/0000-0001-7532-9191

References
1. Prakken B, Albani S and Martini A. Juvenile idiopathic arthritis. Lancet 2011; 377: 2138–2149.
2. Gowdie PJ and Tse SM. Juvenile idiopathic arthritis. Pediatr Clin North Am 2012; 59: 301–327.
3. Weiss JE and Ilowite NT. Juvenile idiopathic arthritis. Pediatr Clin North Am 2005; 52: 413v–442.
4. Barut K, Adrovic A, Sahin S, et al. Juvenile idiopathic arthritis. Balkan Med J 2017; 34: 90–101.
5. Cosickic A, Halilbasic M, Selimovic A, et al. Uveitis associated with juvenile idiopathic arthritis, our observations. Med Arch 2017; 71: 52–55.
6. Clarke SL, Sen ES and Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. Pediatr Rheumatol Online J 2016; 14: 27.
7. Sabri K, Saurenmann RK, Silverman ED, et al. Course, complications, and outcome of juvenile arthritis-related uveitis. J AAPOS 2008; 12: 539–545.
8. Angeles-Han ST, Pelajo CF, Vogler LB, et al. Risk markers of juvenile idiopathic arthritis-associated uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. J Rheumatol 2013; 40: 2088–2096.
9. Moradi A, Amin RM and Thorne JE. The role of gender in juvenile idiopathic arthritis-associated uveitis. J Ophthalmol 2014; 2014: 461078.
10. Castagna I, Roszkowska AM, Alessandrello F, et al. Juvenile idiopathic arthritis-associated uveitis: a retrospective analysis from a centre of South Italy. Int Ophthalmol 2020; 40: 335–342.
11. Heiligenhaus A, Minden K, Foll D, et al. Uveitis in juvenile idiopathic arthritis. Disch Arztebl Int 2015; 112: 92i–100.
12. Ravelli A and Martini A. Juvenile idiopathic arthritis. Lancet 2007; 369: 767–778.
13. Chia A, Lee V, Graham EM, et al. Factors related to severe uveitis at diagnosis in children with juvenile idiopathic arthritis in a screening program. Am J Ophthalmol 2003; 135: 757–762.
14. Grassi A, Corona F, Casellato A, et al. Prevalence and outcome of juvenile idiopathic arthritis-associated uveitis and relation to articular disease. J Rheumatol 2007; 34: 1139–1145.
15. Weiss PF. Diagnosis and treatment of enthesitis-related arthritis. Adolesc Health Med Ther 2012; 2012: 67–74.
16. Walscheid K, Glandorf K, Rothaus K, et al. Enthesitis-related arthritis: prevalence and complications of associated uveitis in children and adolescents from a population-based nationwide study in Germany. *J Rheumatol* 2020; 47: 191085.

17. Edelsten C, Lee V, Bentley CR, et al. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. *Br J Ophthalmol* 2002; 86: 51–56.

18. Dana MR, Merayo-Lloves J, Schaumberg DA, et al. Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. *Ophthalmology* 1997; 104: 236–244.

19. Sen ES and Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. *Clin Immunol* 2020; 211: 108322.

20. Saurenmann RK, Levin AV, Feldman BM, et al. Risk factors for development of uveitis differ between girls and boys with juvenile idiopathic arthritis. *Arthritis Rheum* 2010; 62: 1824–1828.

21. Consolaro A, Giancane G, Alongi A, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. *Lancet Child Adolesc Health* 2019; 3: 255–263.

22. Saurenmann RK, Rose JB, Tyrrell P, et al. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. *Arthritis Rheum* 2010; 62: 1824–1828.

23. Papadopoulou M, Zetterberg M, Oskarsdottir S, et al. Assessment of the outcome of ophthalmological screening for uveitis in a cohort of Swedish children with juvenile idiopathic arthritis. *Acta Ophthalmol* 2017; 95: 741–747.

24. Calandra S, Gallo MC, Consolaro A, et al. Female sex and oligoarthritis category are not risk factors for uveitis in Italian children with juvenile idiopathic arthritis. *J Rheumatol* 2014; 41: 1416–1425.

25. Kodsi SR, Rubin SE, Milojevic D, et al. Time of onset of uveitis in children with juvenile rheumatoid arthritis. *JAAPOS* 2002; 6: 373–376.

26. Sen ES and Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. *Best Pract Res Clin Rheumatol* 2017; 31: 517–534.

27. Abu Samra K, Maghsoudlou A, Roohipoor R, et al. Current treatment modalities of JIA-associated uveitis and its complications: literature review. *Ocul Immunol Inflamm* 2016; 24: 431–439.

28. Haasnoot AJW, Schilham MW, Kamphuis S, et al. Identification of an amino acid motif in hla-drbeta1 that distinguishes uveitis in patients with juvenile idiopathic arthritis. *Arthritis Rheumatol* 2018; 70: 1155–1165.

29. Tappeiner C, Klotsche J, Sengler C, et al. Risk factors and biomarkers for the occurrence of uveitis in juvenile idiopathic arthritis: data from the inception cohort of newly diagnosed patients with juvenile idiopathic arthritis study. *Arthritis Rheumatol* 2018; 70: 1685–1694.

30. Pelegrin L, Casaroli-Marano R, Anton J, et al. Predictive value of selected biomarkers, polymorphisms, and clinical features for oligoarticular juvenile idiopathic arthritis-associated uveitis. *Ocul Immunol Inflamm* 2014; 22: 208–212.

31. Julian K, Terrada C, Quartier P, et al. Uveitis related to juvenile idiopathic arthritis: familial cases and possible genetic implication in the pathogenesis. *Ocul Immunol Inflamm* 2010; 18: 172–177.

32. Maccora I, Sen ES and Ramanan AV. Update on noninfectious uveitis in children and its treatment. *Curr Opin Rheumatol* 2020; 32: 395–402.

33. Lee RW and Dick AD. Current concepts and future directions in the pathogenesis and treatment of non-infectious intraocular inflammation. *Eye (Lond)* 2012; 26: 17–28.

34. Kalinina Ayuso V, Makhotkina N, van Tent-Hoeye M, et al. Pathogenesis of juvenile idiopathic arthritis associated uveitis: the known and unknown. *Surv Ophthalmol* 2014; 59: 517–531.

35. SijsSENS KM, RijkERS GT, Rothova A, et al. Cytokines, chemokines and soluble adhesion molecules in aqueous humor of children with uveitis. *Exp Eye Res* 2007; 85: 443–449.

36. Angeles-Han ST, Yeh S and Vogler LB. Updates on the risk markers and outcomes of severe juvenile idiopathic arthritis-associated uveitis. *Int J Clin Rheumatol* 2013; 8: 83.

37. Ravelli A, Felici E, Magni-Manzoni S, et al. Patients with antinuclear antibody-positive juvenile idiopathic arthritis constitute a homogeneous subgroup irrespective of the course of joint disease. *Arthritis Rheum* 2005; 52: 826–832.

38. Asproudis I, Felekis T, Tsanou E, et al. Juvenile idiopathic arthritis-associated uveitis: data from a region in western Greece. *Clin Ophthalmol* 2010; 4: 343–347.

39. Heiligenhaus A, Foeldvari I, Edelsten C, et al. Proposed outcome measures for prospective
clinical trials in juvenile idiopathic arthritis–associated uveitis: a consensus effort from the multinational interdisciplinary working group for uveitis in childhood. *Arthritis Care Res* (Hoboken) 2012; 64: 1365–1372.

40. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis–associated uveitis. *Arthritis Care Res* (Hoboken) 2019; 71: 703–716.

41. Bou R, Adan A, Borras F, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. *Rheumatol Int* 2015; 35: 777–785.

42. Heiligenhaus A, Michels H, Schumacher C, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. *Rheumatol Int* 2012; 32: 1121–1133.

43. Simonini G, Paudyal P, Jones GT, et al. Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach. *Rheumatology* (Oxford) 2013; 52: 825–831.

44. Papadopoulou C, Kostik M, Bohm M, et al. Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis. *J Pediatr* 2013; 163: 879–884.

45. Wieringa WG, Armbrust W, Legger GE, et al. Efficacy of high-dose methotrexate in pediatric non-infectious uveitis. *Ocul Immunol Inflamm* 2019; 27: 1305–1313.

46. Goebel JC, Roesel M, Heinz C, et al. Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis. *Br J Ophthalmol* 2011; 95: 209–213.

47. Tappeiner C, Roesel M, Heinz C, et al. Limited value of cyclosporine A for the treatment of patients with uveitis associated with juvenile idiopathic arthritis. *Eye* (Lond) 2009; 23: 1192–1198.

48. Bichler J, Benseler SM, Krumrey-Langkammerer M, et al. Leflunomide is associated with a higher flare rate compared to methotrexate in the treatment of chronic uveitis in juvenile idiopathic arthritis. *Scand J Rheumatol* 2015; 44: 280–283.

49. Sobrin L, Christen W and Foster CS. Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. *Ophthalmology* 2008; 115: 1416–2121e1.

50. Miserocchi E, Baltatzis S, Ekong A, et al. Efficacy and safety of chlorambucil in intractable noninfectious uveitis: the Massachusetts Eye and Ear Infirmary experience. *Ophthalmology* 2002; 109: 137–142.

51. Ramanan AV, Dick AD, Benton D, et al. A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial). *Trials* 2014; 15: 14.

52. Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. *N Engl J Med* 2017; 376: 1637–1646.

53. Quartier P, Baptiste A, Despert V, et al. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis–associated anterior uveitis. *Ann Rheum Dis* 2018; 77: 1003–1011.

54. Lee J, Koreishi AF, Zumpf KB, et al. Success of weekly adalimumab in refractory ocular inflammatory disease. *Ophthalmology* 2020; 127: 1431–1433.

55. Liberman P, Berkenstock MK, Burkholder BM, et al. Escalation to weekly adalimumab for the treatment of ocular inflammation. *Ocul Immunol Inflamm* 2020: 1–5.

56. Horton S, Jones AP, Guly CM, et al. Adalimumab in juvenile idiopathic arthritis–associated uveitis: 5-year follow-up of the Bristol participants of the SYCAMORE trial. *Am J Ophthalmol* 2019; 207: 170–174.

57. Cecchin V, Zannin ME, Ferrari D, et al. Longterm safety and efficacy of adalimumab and infliximab for uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2018; 45: 1167–1172.

58. Simonini G, Taddio A, Cattalini M, et al. Prevention of flare recurrences in childhood–refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. *Arthritis Care Res* (Hoboken) 2011; 63: 612–618.

59. Zannin ME, Birolo C, Gerloni VM, et al. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1-year followup data from the Italian Registry. *J Rheumatol* 2013; 40: 74–79.

60. Simonini G, Druce K, Cimaz R, et al. Current evidence of anti-tumor necrosis factor alpha treatment efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach of individual drugs. *Arthritis Care Res* (Hoboken) 2014; 66: 1073–1084.
61. Dhingra N, Morgan J and Dick AD. Switching biologic agents for uveitis. *Eye (Lond)* 2009; 23: 1868–1870.

62. William M, Faez S, Papaliodis GN, *et al.* Golimumab for the treatment of refractory juvenile idiopathic arthritis-associated uveitis. *J Ophthalmic Inflamm Infect* 2012; 2: 231–233.

63. Palmou-Fontana N, Calvo-Rio V, Martin-Varillas JL, *et al.* Golimumab in refractory uveitis associated to juvenile idiopathic arthritis: multicentre study of 7 cases and literature review. *Clin Exp Rheumatol* 2018; 36: 652–657.

64. Sepah YJ, Sadiq MA, Chu DS, *et al.* Primary (month-6) outcomes of the stop-uveitis study: evaluating the safety, tolerability, and efficacy of tocilizumab in patients with noninfectious uveitis. *Am J Ophthalmol* 2017; 183: 71–80.

65. Calvo-Rio V, Santos-Gomez M, Calvo I, *et al.* Anti-interleukin-6 receptor tocilizumab for severe juvenile idiopathic arthritis-associated uveitis refractory to anti-tumor necrosis factor therapy: a multicenter study of twenty-five patients. *Arthritis Rheumatol* 2017; 69: 668–675.

66. Tappeiner C, Mesquida M, Adan A, *et al.* Evidence for tocilizumab as a treatment option in refractory uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2016; 43: 2183–2188.

67. Ramanan AV, Dick AD, Jones AP, *et al.* A phase II trial protocol of Tocilizumab in anti-TNF refractory patients with JIA-associated uveitis (the APTITUDE trial). *BMC Rheumatol* 2018; 2: 4.

68. Quesada-Masachs E and Caballero CM. Subcutaneous tocilizumab may be less effective than intravenous tocilizumab in the treatment of juvenile idiopathic arthritis-associated uveitis. *J Rheumatol* 2017; 44: 260–261.

69. Zulian F, Balzarini M, Falcini F, *et al.* Abatacept for severe anti-tumor necrosis factor alpha refractory juvenile idiopathic arthritis-related uveitis. *Arthritis Care Res (Hoboken)* 2010; 62: 821–825.

70. Kenawy N, Cleary G, Mewar D, *et al.* Abatacept: a potential therapy in refractory cases of juvenile idiopathic arthritis-associated uveitis. *Graefe's Arch Clin Exp Ophthalmol* 2011; 249: 297–300.

71. Tappeiner C, Misericocchi E, Bodaghi B, *et al.* Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2015; 42: 706–711.

72. Birolo C, Zannin ME, Arsenyeva S, *et al.* Comparable efficacy of abatacept used as first-line or second-line biological agent for severe juvenile idiopathic arthritis-related uveitis. *J Rheumatol* 2016; 43: 2068–2073.

73. Bauermann P, Heiligenhaus A and Heinz C. Effect of Janus Kinase inhibitor treatment on anterior uveitis and associated macular edema in an adult patient with juvenile idiopathic arthritis. *Ocul Immunol Inflamm* 2019; 27: 1232–1234.

74. Misericocchi E, Giuffre C, Cornalba M, *et al.* JAK inhibitors in refractory juvenile idiopathic arthritis-associated uveitis. *Clin Rheumatol* 2020; 39: 847–851.

75. Heiligenhaus A, Misericocchi E, Heinz C, *et al.* Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab). *Rheumatology (Oxford)* 2011; 50: 1390–1394.

76. Misericocchi E, Pontikaki I, Modorati G, *et al.* Rituximab for uveitis. *Ophthalmolog* 2011; 118: 223–224.

77. Misericocchi E, Modorati G, Berchicci L, *et al.* Long-term treatment with rituximab in severe juvenile idiopathic arthritis-associated uveitis. *Br J Ophthalmol* 2016; 100: 782–786.

78. Simonini G, Bracaglia C, Cattalini M, *et al.* Predictors of relapse after discontinuing systemic treatment in childhood autoimmune chronic uveitis. *J Rheumatol* 2017; 44: 822–826.

79. Heinz C, Mingels A, Goebel C, *et al.* Chronic uveitis in children with and without juvenile idiopathic arthritis: differences in patient characteristics and clinical course. *J Rheumatol* 2008; 35: 1403–1407.

80. Vitale AT, Graham E and de Boer JH. Juvenile idiopathic arthritis-associated uveitis: clinical features and complications, risk factors for severe course, and visual outcome. *Ocul Immunol Inflamm* 2013; 21: 478–485.

81. Kalinina Ayuso V, van de Winkel EL, Rothova A, *et al.* Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. *Am J Ophthalmol* 2011; 151: 217–222.

82. Thomas AS. Biologics for the treatment of noninfectious uveitis: current concepts and emerging therapeutics. *Curr Opin Ophthalmol* 2019; 30: 138–150.

83. Schmeling H and Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2005; 44: 1008–1011.

84. Smith JA, Thompson DJ, Whitcup SM, *et al.* A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. *Arthritis Rheum* 2005; 53: 18–23.
85. De Benedetti F, Robbioni P, Massa M, et al. Serum interleukin-6 levels and joint involvement in polyarticular and pauciarticular juvenile chronic arthritis. *Clin Exp Rheumatol* 1992; 10: 493–498.

86. Yoshimura T, Sonoda KH, Ohguro N, et al. Involvement of Th17 cells and the effect of anti-IL-6 therapy in autoimmune uveitis. *Rheumatology (Oxford)* 2009; 48: 347–354.

87. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005; 353: 1114–1123.

88. Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008; 372: 383–391.

89. Sherrer Y. Abatacept in biologic-naive patients and TNF inadequate responders: clinical data in focus. *Curr Med Res Opin* 2008; 24: 2283–2294.

90. Taylor PC. Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis. *Rheumatology (Oxford)* 2019; 58: i17–i26.

91. Flanagan ME, Blumenkopf TA, Brissette WH, et al. Discovery of CP-690,550: a potent and selective Janus kinase (JAK) inhibitor for the treatment of autoimmune diseases and organ transplant rejection. *J Med Chem* 2010; 53: 8468–8484.

92. Meyer DM, Jesson MJ, Li X, et al. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. *J Inflamm (Lond)* 2010; 7: 41.

93. Parikh JG, Tawansy KA and Rao NA. Immunohistochemical study of chronic nongranulomatous anterior uveitis in juvenile idiopathic arthritis. *Ophthalmology* 2008; 115: 1833–1836.

94. Ruperto N, Brunner HI, Quartier P, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012; 367: 2396–2406.

95. Giancane G, Minoia F, Davi S, et al. IL-1 inhibition in systemic juvenile idiopathic arthritis. *Front Pharmacol* 2016; 7: 467.

96. Haasnoot AM, Kuiper JJ, Hiddingh S, et al. Ocular fluid analysis in children reveals interleukin-29/interferon-lambda1 as a biomarker for juvenile idiopathic arthritis-associated uveitis. *Arthritis Rheumatol* 2016; 68: 1769–1779.