Update on biologic therapies for juvenile idiopathic arthritis-associated uveitis

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Abstract

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood, and juvenile idiopathic associated uveitis (JIA-U) is the most frequently noted extra-articular manifestation. JIA-U can present asymptptomatically and lead to ocular complications, so regular screening and monitoring are needed to prevent potentially sight-threatening sequelae. Topical glucocorticoids such as prednisolone acetate are usually the first line of treatment for anterior uveitis associated with JIA-U, but long-term use may be associated with cataract, ocular hypertension and glaucoma. Disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate allow tapering of the corticosteroids to prevent long-term complications. Biologic therapies have been increasingly used as targeted therapies for JIA-U, particularly monoclonal antibodies targeting the proinflammatory cytokine TNF-α such as adalimumab and infliximab. One recent, multicenter, prospective, randomized clinical trial provided evidence of the efficacy of adalimumab with methotrexate for JIA-U compared to methotrexate alone. Another clinical trial studying the interleukin-6 inhibitor tocilizumab for JIA-U showed promise in tapering topical corticosteroids. Additionally, JAK inhibitors are emerging biologic therapies for JIA-U in patients.
refractory to TNF-α inhibitors, with a clinical trial assessing the efficacy of baricitinib for JIA-U underway. While clinical trials on these novel biologics are limited, further investigation of these agents may provide additional therapeutic options for JIA-U.

**Keywords**

Juvenile idiopathic arthritis (JIA); uveitis; biologics; tumor necrosis factor alpha; uveitis; pediatric uveitis; JAK inhibitor

**Introduction**

Juvenile idiopathic arthritis (JIA), previously known as juvenile rheumatoid arthritis (JRA), is the most common rheumatic disease of childhood. The onset of JIA is before age 16, and arthritis is present for a minimum of 6 weeks (1). The most common extra-articular manifestation of JIA is uveitis (JIA-U), which involves inflammation of the uvea comprising the iris, ciliary body, and choroid, and this occurs in up to 20% of children with JIA. JIA-U is the most common cause of non-infectious uveitis in childhood. More broadly, non-infectious uveitis is one of the leading causes of preventable blindness in the United States while also accounting for 15% of the cases of blindness in Western countries (2).

Nearly 21% of all cases of childhood uveitis in the United States have an associated diagnosis of JIA-U while the prevalence of JIA-U in bilateral pediatric uveitis cases in the United States is 89% (3). However, there is significant variation in the prevalence worldwide (4,5). Ocular complications and vision loss have been noted in 3–66% of children with JIA-U with up to 25% of children with JIA-U progressing to blindness (6). Given the severity of the disease and its association with an increased prevalence of blindness in Western countries, regular ophthalmic screening of children with JIA, stratification of risk by JIA subtype, and timely, effective treatment are needed in order to prevent the sequelae of JIA-U that may lead to visual impairment.

This review focuses on standard treatments as well as promising biologic therapies of JIA-U. Although synthetic treatments are commonly administered and have demonstrated efficacy, adverse effects and treatment-refractory disease may require biologic alternatives. With the emergence of biologic therapies with targeted mechanisms, a broad understanding of their efficacy as JIA-U treatment and safety profiles are needed to provide the full complement of therapies for multidisciplinary care from rheumatologists and ophthalmologists.

**Clinical presentation**

JIA-U can be classified based on the Standardization of Uveitis Nomenclature (SUN) guidelines by specific anatomic location of inflammation: anterior, intermediate, and posterior. Panuveitis involves inflammation of all three of these locations (7). In addition, uveitis can be stratified based on time course into acute, subacute, chronic, or recurrent. The most common form of JIA-U is chronic anterior uveitis with JIA-U accounting for 75% of all pediatric anterior uveitis cases (8). General ocular symptoms may include redness, pain, photophobia, excessive tearing, and floaters (9). Anterior uveitis can present with corneal
findings (keratic precipitates) and pupillary changes (e.g., posterior synechiae) with dense white cataract in some individuals (10). Chronic anterior uveitis, however, often presents asymptptomatically, which may delay diagnosis and subsequent treatment, thereby increasing the risk of ocular complications.

**Screening**

Since an asymptomatic presentation can occur and children may have difficulty reporting ocular changes, regular screenings are vital for detection of JIA-U. Various ophthalmic screening guidelines exist, and most include a slit lamp examination, which allows for examination of the anterior segment and posterior segment including the retina and choroid. The American College of Rheumatology/Arthritis Foundation (ACR/AF) guidelines for ophthalmic screening of children with JIA-U recommend ophthalmic screenings every 3 months in patients with JIA with a high risk of developing associated uveitis (11). This frequency is based on the underlying risk factors for JIA-U. The American Academy of Pediatrics (AAP) lists these risk factors for JIA-U as ANA seropositivity, oligoarticular or polyarticular JIA subtypes, early age of onset (≤6 years), and ≤4 years duration of JIA (12). JIA-U also has a female predominance, and an association with HLA-DR8 is a risk factor although this does not inform the screening schedule (13–15). Uveitis is diagnosed based on the presence of inflammatory features including cells in the anterior chamber (AC) defined by the SUN grading criteria as well as AC flare from protein leakage (7,16,17).

**Monitoring**

Following a diagnosis of JIA-U, continued ophthalmic monitoring for inflammation and disease complications remains critical. The frequency of visits is based on disease severity, ocular complications, and treatment (11,18). In addition, continuous and frequent monitoring is especially needed when tapering medications to gauge relapses or increases in uveitis activity. While tapering or discontinuing topical glucocorticoids, ACR/AF strongly recommends ophthalmic monitoring within 1 month of each change in topical glucocorticoids (11). If tapering or discontinuing systemic therapy, monitoring is strongly recommended within 2 months of changing the regimen. If the patient is on stable therapy, monitoring can be reduced to every 3 months.

Continued monitoring of intraocular pressure (IOP) is vital in patients with JIA-U because of the increased risk of glaucoma and ocular hypertension (6,19). Angeles-Han *et al.* (6) reported other ocular complications including cataract (31%), synechiae (31%), band keratopathy (25%), and cystoid macular edema (CME) (15%). Regular assessment of AC cells and new or worsening ocular complications can provide monitoring of visual damage as well as show efficacy of treatment. Risk factors for visual impairment include increased severity of JIA-U and uveitis onset preceding arthritis (15,20). A retrospective cohort study by Thorne *et al.* (21) showed posterior synechiae, AC flare ≥1+, and abnormal IOP at presentation were risk factors for vision loss in patients with JIA-U. In follow-up visits, AC cells of ≥0.5+ was associated with an increased risk of visual impairment and blindness. To minimize the occurrence of these ocular complications related to JIA-U, early screening, diagnosis, and treatment are needed for this patient population.
Pathogenesis

While there is evidence showing an association between JIA and uveitis, the initiating events of uveitis immunopathology are not well understood. A combination of genetic and environmental factors is thought to contribute to its occurrence. Studies have shown an association within the human leukocyte antigen (HLA) area and have looked at the function of the various HLA alleles on the development of JIA (22,23). Specifically, combinations of HLA-DRB1 genes in children with JIA may predispose them to uveitis development (24). In addition, the current hypothesis proposes that both adaptive (antigen-specific) and innate (non-specific) responses contribute to uveitis (25). Uveitis may be caused by a loss of tolerance to auto-antigens and the activation of T lymphocytes (26). CD4+ cells (Th1, Th2, Th17) and CD8+ cells may also play an important role in autoimmune uveitis (23).

Various factors are critical in the inflammatory process. TNF-α is synthesized by monocytes, neutrophils, mast cells, macrophages, and both natural killer and T cells, and it drives Th1 cell responses (27,28). Increased expression of TNF-α has also been shown in experimental autoimmune uveitis at peak levels of inflammation (29). IL-6 is a cytokine derived from macrophages, which can function in both a pro- and anti-inflammatory fashion. It has been shown to play a role in the differentiation and proliferation of T cells (28,30,31). Janus kinase (JAK) mediated pathways are also involved in the pathogenesis of several autoimmune diseases including uveitis (32). All of these are vital players in the perpetuation of inflammation, and therapies may target these specific factors to limit the inflammation and ocular sequelae from JIA-uveitis.

Treatment

Synthetic treatment

Early detection and treatment are necessary to optimize the visual outcomes of children with JIA-U. The goal of treatment is to achieve inactive uveitis or an AC cell grade of 0 (33). Topical glucocorticoids (e.g., prednisolone acetate 1% or difluprednate 0.05%) are the first line of treatment for anterior uveitis and are used in 90% of patients with JIA-U (34,35). There are, however, adverse effects associated with long-term glucocorticoid use such as ocular hypertension and development of cataract (36). Prednisolone acetate is preferred before difluprednate (Durezol) because of increased adverse effects of difluprednate (37). However, increased disease severity may prompt the use of difluprednate in some patients but requires close monitoring for IOP-related adverse events, which has been shown to be common in individuals receiving difluprednate (38).

Local triamcinolone acetonide (TA) injections have also demonstrated efficacy, but local periocular or intravitreal injections may require general anesthesia for pediatric patients and require repeated administration, leading to increased risk for glaucoma and cataract development (34). Longer duration implants have also been explored to reduce the administration of medication. Dexamethasone 0.7 mg intravitreal insert (Ozurdex, Allergan) and fluocinolone acetonide 0.59 mg surgical intravitreal implant (Retisert, Bausch and Lomb) have shown efficacy in cases of refractory JIA-U but are associated with an increase in IOP and cataract formation, particularly with the Retisert implant (39–41). In general,
glucocorticoid injections and implants are not recommended in children with JIA-U. Oral glucocorticoids may be used as bridging therapy but not for prolonged use.

Because of the adverse effects associated with prolonged corticosteroid use, disease modifying anti-rheumatic drugs (DMARDS) are commonly prescribed to patients with JIA-U. Methotrexate (10–25 mg/m²) administered orally or via subcutaneous injection is the most common first-line systemic agent, which is prescribed for 76% of patients with JIA-U (34,35,42). Methotrexate is an anti-metabolite that inhibits DNA replication and RNA transcription in B and T lymphocytes (43,44). Common adverse effects include gastrointestinal (GI) toxicity (oral ulcers, nausea, vomiting) and hepatorenal toxicity, so patients taking methotrexate should have regular lab monitoring for disease toxicity (34). Subcutaneous administration of methotrexate has a higher bioavailability and may minimize gastrointestinal side effects (42).

Other synthetic DMARDS are mycophenolate mofetil (MMF) and cyclosporine A (CsA) although these are prescribed less frequently for JIA-U as they are less effective for arthritis (45,46). MMF has similar GI toxicity effects as methotrexate in addition to hair loss and leukopenia. CsA, a T-cell calcineurin inhibitor, has been shown to cause nephrotoxicity and hirsutism as well as similar GI toxicity and hepatotoxicity as methotrexate (34), but it is less frequently prescribed in clinical practice (47).

**Biologic treatment**

**TNF-α inhibitors**—Biologic therapies are effective for children with JIA-U that is severe or refractory to methotrexate. TNF-α has been targeted to control the inflammatory response in JIA-U (Table 1), and adalimumab is a common anti-TNF-α prescribed for JIA-U refractory to methotrexate or severe in presentation. The SYCAMORE trial (Table 2) is a multicenter, double blind, randomized, placebo-controlled trial analyzing the efficacy of adalimumab with methotrexate for JIA-U (48). The standard dose of methotrexate given was 10 to 20 mg per square meter with a maximum dose of 25 mg. The subcutaneous adalimumab dose was 20 mg in patients weighing <30 kg or 40 mg in patients weighing ≥30 kg. During an interim analysis, adalimumab with methotrexate showed a significantly lower risk of treatment failure than the placebo-control group, and the trial recruitment was held due to these efficacy signals. However, adalimumab was associated with an increase in adverse effects compared to the control group, with some of these adverse effects including infections, gastrointestinal disorders, and respiratory disorders. A meta-analysis conducted by Jari et al. assessed the efficacy of adalimumab in 1,289 patients, and the pooled response rate of adalimumab was estimated to be 68.0% (95% CI: 65.4 to 70.6). Common side effects recorded in this meta-analysis included local pain, anemia, cataracts, and uveitis flares (49).

Infliximab is an anti-TNF-α treatment that is also commonly utilized for JIA-U. Infliximab has demonstrated efficacy for JIA-U when administered at high dosages (10–20 mg/kg/dose) with good tolerability (51,52). However, there has been variability in the dosing of infliximab and limited studies analyzing efficacy and safety, which may lead to differences in outcomes seen (34). In a retrospective study by Lerman et al. the efficacy of infliximab, adalimumab and etanercept were analyzed to note if minimal or no uveitis activity could be obtained with these treatments (50). Participants treated with infliximab had a median
starting dose of 9.3 mg/kg (range 4.5 to 13.3 mg/kg) with only 5 subjects receiving treatment with doses <7 mg/kg. All participants treated with adalimumab received 40 mg every other week. Participants on etanercept received between 12.5–25 mg twice weekly, except for one small young child who received 0.8 mg/kg weekly. Treatment success was observed in 75% of patients overall, and there were better outcomes if diagnosed with JIA. In addition, adalimumab and infliximab were shown to be more effective than etanercept. A meta-analysis of anti-TNF-α on efficacy of childhood chronic uveitis has demonstrated superior efficacy with adalimumab and infliximab compared to etanercept, with the assertion that current evidence does not support the use of etanercept for JIA-U although evidence is limited (41,70,71).

**IL-6 targets**—IL-6 inhibitors can be considered for patients refractory to anti-TNF-α treatments (Table 1). These therapies are shown to be effective for rheumatoid arthritis especially since levels of IL-6 have been shown to correlate to disease severity (72,73). Based on this, the efficacy of IL-6 targets to treat JIA-U has been explored. Tocilizumab, a monoclonal antibody inhibitor of IL-6 receptor, is approved for treatment of JIA, and the standard dose is 8 mg/kg at 4-week intervals. Retrospective and limited prospective studies have shown efficacy in uveitis (31,53–55). Tocilizumab has been shown especially effective in pediatric patients with CME who are otherwise refractory to treatment (56,57). A multicenter, Phase 2 trial (APTITUDE study) (Table 2) assessed the efficacy of tocilizumab in 21 children with JIA-U who were refractory to methotrexate and TNF-α inhibitors (54). Participants continued a stable dose of methotrexate throughout the trial. Those weighing ≥30 kg were dosed with 162 mg of tocilizumab every 2 weeks while participants weighing <30 kg were dosed with 162 mg of tocilizumab every 3 weeks through a subcutaneous injection. The study did not meet its primary endpoint as 7 patients showed a response, but it did show promise as corticosteroid drops were tapered or stopped in several patients and resolution of three out of the four macular edema cases did occur. Adverse effects associated with administration of tocilizumab include autoimmune cytopenia, gastrointestinal toxicity, allergic reactions, and increased infections (55,58).

Another monoclonal antibody IL-6 inhibitor that shows potential in non-infectious uveitis is sarilumab. This therapy did show improvement in patients with non-infectious uveitis in the SATURN study, a Phase 2 study analyzing the efficacy and safety of sarilumab in adults. In this study, patients received treatment every 2 weeks for 16 weeks with subcutaneous sarilumab 200 mg or placebo. However, no similar studies have been conducted focusing on JIA-U (59). Side effects for sarilumab include neutropenia and elevated alanine-aminotransferase levels. Other IL-6 inhibitors are on the market; however, these have not been studied yet in terms of JIA-U or non-infectious uveitis.

**Cell surface receptor targets**—Abatacept (Table 1) is another biologic therapy that decreases CD80/CD86 expression on B-cells and prevents the activation of T cells. The standard dose is 10 mg/kg at weeks 0, 2, and 4 and then monthly (74). A prospective study of two patients with JIA-U who were refractory to maximum conventional treatment received IV abatacept at 10 mg/kg monthly. After 9 months, both patients remained in remission without steroids, but joint disease remained active in one of the cases. Abatacept
is a promising treatment for refractory cases of JIA-uveitis, but concomitant therapies may be necessary to control the articular disease (60,61). A multinational retrospective study comparing abatacept as a first-line treatment and as a rescue treatment showed that the use of abatacept as a first line therapy was comparable to rescue treatment in refractory JIA-U (62). Side effects associated with abatacept can include nasopharyngitis, respiratory infections, and gastrointestinal toxicity (nausea), and in some studies, an exacerbation of the JIA-U has been seen with the use of abatacept (63,64).

Rituximab (Table 1) targets the CD20 antigen of B cells, which help promote differentiation of T regulatory cells (75). Standard dose of rituximab is a 1,000 mg/infusion on days 1 and 15 and then every 6 months (74). A retrospective multicenter study analyzed 10 patients with severe refractory JIA-U (65). Uveitis did improve in seven patients given rituximab (375 mg/m² body surface) and allowed the tapering of glucocorticoids and DMARDs. However, new uveitis occurred in 4 of the 7 after 6–9 months. These recurrences were attributed to the survival of long-lived autoreactive plasma cells without the CD20 antigen because of B-cell depletion (65,66). A study by Misericocchi showed the efficacy of rituximab in eight patients who were refractory to three different TNF-α inhibitors with seven of them achieving persistent remission with tapered down cDMARDs (67). In this study, rituximab was given at the dose of 1,000 mg per infusion on days 1 and 15. While rituximab does show promise for treatment of refractory JIA-U, there have been varying reports on efficacy, and further studies are needed.

**Janus kinase inhibitors (JAK inhibitors)—** Despite a broad array of therapeutics available, some patients do not attain remission of their uveitis, and JAK inhibitors (Table 1) have emerged as another class of immunomodulatory therapies for these individuals. While evidence of JAK inhibition in the treatment of JIA-U is limited, Misericocchi et al. describes the use of JAK inhibitor therapies in four children with JIA-U refractory to other therapies such as infliximab, adalimumab, rituximab, abatacept and tocilizumab (32). Three cases were treated with baricitinib (4–5 mg/day) while one case used tofacitinib (5 mg, twice daily) as a therapy. All patients showed improvement of uveitis activity and control of intraocular inflammation; however, articular disease did not respond as favorably as the ophthalmic inflammation. In addition, the treatment was well tolerated in patients, and no systemic side effects, lab anomalies, or infections were noted in the 7-month follow-up period. Another report showed a positive effect of tofacitinib (5 mg, twice daily) in a patient with JIA-U and refractory macular edema (ME) (68). The role of JAK inhibition for refractory cases of JIA-U is unknown but requires further investigation. Currently, there is a clinical trial studying the efficacy of baricitinib in pediatric patients with JIA-U (69).

**Relapse and remission**

In recent years, there has been increased interest in understanding relapse and remission rates following discontinuation of immunomodulatory therapies (IMT). A retrospective case series found that 69% (8/13) patients treated with methotrexate relapsed after discontinuation of therapy. Predictors of relapse free survival according to this study included patient’s age >8 at withdrawal and inactivity of uveitis >2 years prior to withdrawal (76). Another study found that patients treated with IMT at an older age and later in their
disease course had higher rates of relapse, often within one year of medication discontinuation (77).

A retrospective, multicenter, cohort study by Simonini et al. showed time to achieve inactivity was predictive of remission success in patients with JIA-U (78). Also, achieving inactivity and remission by anti-TNF-α compared to methotrexate therapies was predictive of a lower chance of remission after systemic treatment was discontinued. While another study showed a longer period of inactivity prior to withdrawal of methotrexate reduced the chances of relapse, this was not replicated by Simonini et al. (76,78).

A retrospective study conducted by Acharya et al. analyzed the relapse rates after discontinuation of IMT especially in cases of TNF-α inhibitors (79). Patients were separated based on their reason for discontinuation delineating those who stopped due to presumed remission versus other reasons. The study found that while corticosteroid-sparing treatment was achieved in a majority of the patients, the attempts to discontinue IMT were often unsuccessful. This study raised additional key questions regarding the appropriate timing of medication discontinuation and relapse rate. These questions will be assessed in the National Eye Institute-funded multicenter Adalimumab in JIA-associated Uveitis Stopping Trial, or ADJUST Study, a Phase 3 clinical trial analyzing the feasibility of discontinuing adalimumab in patients with JIA-U (80).

**Conclusions**

Uveitis is a common manifestation of JIA-U, but ocular complications that lead to vision loss may be prevented with regular screening and timely, effective therapy. JIA-U typically presents asymptotically, thus early scheduled screening is critical. Prompt treatment and control of inflammation can improve visual outcomes and prevent vision loss. An improved understanding of the growing array of medications is needed for appropriate therapeutic choice. Methotrexate is the first-line corticosteroid-sparing treatment, but refractory uveitis, severe disease at onset, side effects, and intolerance may preclude its use in some patients.

Biologic therapies targeting inflammatory mechanisms are alternative treatments, which are increasingly used in clinical practice. TNF-α inhibitors such as adalimumab and infliximab are often the initial choices for biologic therapy for children with severe uveitis at onset or methotrexate failure. In patients refractory to anti-TNF-α factors, other biologics such as tocilizumab and abatacept may also be considered. In addition, emerging therapies targeting cell surface markers involved in the inflammatory cascade show promise especially for refractory cases but requires additional investigation. Further identification and study of inflammatory biomarker profiles are needed to develop targeted anti-inflammatory measures for patients with JIA-U.

**Acknowledgments**

**Funding:**

This project was supported by unrestricted departmental grant from Research to Prevent Blindness, Inc. to the Emory Eye Center, Emory University School of Medicine, National Eye Institute/National Institutes of Health core grant P30-EY006360 (Department of Ophthalmology, Emory University School of Medicine), National Eye Institute.
of the National Institutes of Health under award number K23 EY030158 (Shantha), R01EY030521 (STAH), and R01 EY029594 (SY). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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## Table 1

| Class                  | Drug         | Dose                                                                 | Side-effects                                                                 | Evidence                                                                 |
|------------------------|--------------|-----------------------------------------------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| TNF-α inhibitors       | Adalimumab   | <30 kg (20 mg every 2 weeks); ≥30 kg (40 mg every 2 weeks). ^1 Higher than standard JIA doses may be needed—weekly endorsed by CARRA and ACR/AF (42) | Infections, gastrointestinal disorders, respiratory disorders, cataracts. Anti-TNF antibodies, reactivation of latent tuberculosis | RCT shows efficacy especially in addition to methotrexate. Retrospective studies demonstrating efficacy (48–50) |
|                        | Infliximab   | 10–20 mg/kg monthly                                                   | Infusion reactions, anti-TNF antibodies, reactivation of latent tuberculosis  | Retrospective studies show efficacy at high doses (34,50–52)               |
| IL-6 inhibitors        | Tocilizumab  | 8 mg/kg at 4-week intervals. ^1 Higher than standard JIA doses may be needed—dose every 2 weeks, not endorsed yet | Gastrointestinal toxicity, allergic reactions, autoimmune cytopenia          | RCT did not meet primary end point but did show promise especially for tapering of corticosteroids. Retrospective and limited prospective studies show efficacy especially in patients with cystoid macular edema (31,53–58) |
|                        | Sarilumab    | 200 mg                                                               | Neutropenia, elevated alanine-amino-transferase levels                      | RCT in adults showed efficacy, but no similar study in pediatric patients (59) |
| Cell surface receptor  | Abatacept    | 10 mg/kg at weeks 0, 2, 4 and then monthly                           | Nasopharyngitis, respiratory infections, gastrointestinal toxicity           | Prospective study of 2 patients refractory to conventional treatment achieved remission without steroids. Retrospective study showed efficacy in refractory cases (60–64) |
| targets                | Rituximab    | 1,000 mg/infusion on days 1 and 15 and then every 6 months          | Infusion reaction, neutropenia                                             | Varying reports on efficacy. Retrospective study showed efficacy in severely refractory cases, but there were recurrences (65–67) |
| JAK inhibitor          | Tofacitinib  | 5 mg, twice daily in study                                           | No systemic side effects noted in study                                    | Efficacy shown in a case study in patient refractory to other therapies and another case in a patient with macular edema (32,68) |
|                        | Baricitinib  | 4–5 mg/day in study                                                  | No systemic side effects noted in study                                    | Efficacy shown in 3 patients refractory to other therapies. Clinical trial in progress (32,69) |

*used in practice but not in official guidelines yet. JIA-U, juvenile idiopathic associated uveitis; JAK, janus kinase.
### Table 2

Recent clinical trials in pediatric uveitis

| Medication and study | Disease indication                  | Design                                                   | Patients recruited | Treatment arms                                                                 | Efficacy outcome                                                                 | Safety                                      |
|----------------------|------------------------------------|----------------------------------------------------------|-------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------|
| Adalimumab (SYCAMORE Trial) | JIA-U patients taking methotrexate | Multi-center, double blind, randomized, placebo controlled (48) | 90 (originally meant to be 114, but prespecified stopping criteria were met) | Assigned 2:1 ratio for adalimumab; 20 mg every 2 weeks if <30 kg; 40 mg every 2 weeks if ≥80 kg | Treatment with adalimumab significantly delayed the time to treatment failure as compared with methotrexate along | Minor infections and respiratory disorders |
| Tocilizumab (APTITUDE Study) | JIA-U refractory to both methotrexate and TNF inhibitors | Multi-center, single-arm, phase 2 trial (54) | 21 | 162 mg every 3 weeks if <30 or every 2 weeks ≥80 kg | Primary endpoint not met but several patients responded to treatment | Injection site reaction, arthralgia, headache |

JIA-U, juvenile idiopathic associated uveitis.