CHAPTER

2

Uveitis associated with juvenile idiopathic arthritis

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**ABSTRACT**

Juvenile idiopathic arthritis (JIA) is the most common cause of uveitis in children. While symptoms are usually mild, persistent eye inflammation could lead to severe complications and impaired vision. It is essential that JIA patients at risk are diagnosed with uveitis early, receive adequate treatment, and avoid developing complications, such as cataract, glaucoma and amblyopia. The purpose of this mini-review is to summarize the screening strategies and clinical management for JIA-associated uveitis (JIA-U) as well as the current state of molecular markers linked to this condition. Because glaucoma is one of the most common causes of visual loss in JIA-U, special focus will be put on this serious complication. We conclude by describing the current evidence regarding to the long-standing question whether chronic anterior uveitis without arthritis may be the same disease entity as JIA-U.
EPIDEMIOLOGY

Uveitis primarily affects adults, with children accounting for approximately 5–10% (Edelsten et al. 2003). Most pediatric cases (69-95%) in developed countries are non-infectious, and often occur in conjunction with other systemic inflammatory conditions. About half of all cases (41 to 47%) are associated with Juvenile Idiopathic Arthritis (JIA), the most prevalent disease in children with uveitis (Edelsten et al. 2003; de Boer, Wulffraat, and Rothova Br 2003; Hettinga et al. 2015).

A meta-analysis from 2019 reported an approximate incidence of uveitis in JIA (JIA-U) of 13%, varying from 19% in Northern European countries to 5% in Southeast Asia (Hayworth et al. 2019). There is uncertainty about whether geographical variation in uveitis prevalence among JIA cases is caused by genetic factors, environmental factors, or differences in uveitis screening practices (Sen and Ramanan 2020). Uveitis prevalence also varies considerably between disease categories of JIA, which is mostly absent in patients with systemic arthritis and rheumatoid factor-positive polyarthritis, but may affect half of the cases with oligoarthritis in some cohort studies (van Straalen et al. 2021). The incidence of uveitis is higher in female JIA patients, which is not an independent predictor variable, but rather related to a positive antinuclear antibodies (ANA) status and onset of oligoarthritis at young age (van Straalen et al. 2022; 2021; Tappeiner et al. 2018). JIA-U development is most likely in the first four years after arthritis onset, but cases have been reported even after ten years (van Straalen et al. 2021; Heiligenhaus et al. 2007). About 10% of children are first diagnosed with uveitis, with JIA developing later (Sen and Ramanan 2020; Heiligenhaus et al. 2007; Sen, Dick, and Ramanan 2015).

CLINICAL PRESENTATION

The most common form of JIA-U is chronic non-granulomatous anterior uveitis, which is often asymptomatic in the early stages of the disease. Uveitis usually occurs bilaterally, involving both eyes simultaneously or starting unilaterally and rapidly followed by inflammation in the other eye within a few months. Patients can suffer from severe inflammation in both eyes or have a different severity in each eye. During active uveitis, a mild to moderate degree of fine anterior chamber cells are present, with or without non-granulomatous keratic precipitates or fine endothelial inflammatory deposits. A less typical manifestation of active JIA-U is the presence of granulomatous keratic precipitates and posterior segment involvement (Vitale, Graham, and de Boer 2013).
In contrast, acute anterior uveitis is characterized by significant symptoms, including a painful red eye and moderate to marked anterior chamber cells, and tends to occur in individuals with enthesitis-related arthritis who test positive for HLA-B27 (±15% of JIA-U cases) (Sen and Ramanan 2020; Sen, Dick, and Ramanan 2015).

SCREENING

Regular ophthalmologic screening of JIA patients is essential for detecting and treating chronic anterior uveitis at an early stage, thereby preventing vision-threatening complications including cataracts, synechiae and glaucoma (Clarke, Sen, and Ramanan 2016; Heiligenhaus et al. 2007; Sen, Dick, and Ramanan 2015). This screening involves a combination of age-appropriate visual acuity testing, measurement of intraocular pressure and slit lamp examination by the ophthalmologist, and should commence shortly after onset of arthritis (Sen, Dick, and Ramanan 2015; Sen and Ramanan 2020; Clarke, Sen, and Ramanan 2016). Following a 2007 nation-wide study, the German Uveitis in Childhood Study Group proposed a set of screening frequencies for JIA-U based on the current International League of Associations for Rheumatology’s categories of JIA, ANA status, age at JIA onset, and JIA disease duration (Heiligenhaus et al. 2007). This study also identified patients at a relatively low, intermediate and high risk for JIA-U, with a recommended screening interval of three months for the high risk group and less frequent screening intervals for the other risk groups (Figure 2.1). Although these recommendations are widely adopted, some have suggested adhering to shorter intervals for the first six months (every 2 months) following arthritis onset in patients with JIA who are most likely to develop uveitis (i.e., highest risk group)(Chia et al. 2005), in line with previous guidelines, including the 2006 British Society for Pediatric and Adolescent Rheumatology (BSPAR)/Royal College of Ophthalmology screening guidelines (Clarke, Sen, and Ramanan 2016; Sen and Ramanan 2020; Sen, Dick, and Ramanan 2015)(but not the 2019 American College of Rheumatology/Arthritis Foundation screening guidelines (Angeles-Han, Ringold, et al. 2019b). The BSPAR guidelines also recommend bimonthly screening for the duration of six months after tapering or discontinuing immunosuppressive drugs for treating arthritis, such as methotrexate. Also, patients should be advised to monitor their unilateral vision regularly after discharge from screening, and when to seek medical attention (Clarke, Sen, and Ramanan 2016; Sen and Ramanan 2020; Sen, Dick, and Ramanan 2015). In the near future, screening frequencies might be guided by more personalized prediction models that include molecular data such as inflammatory and genetic biomarkers, including erythrocyte sedimentation rate, S100A12, and the YST-amino acid motif in the HLA-DRB1 gene (Tappeiner et al. 2018; Haasnoot, Kuiper, and de Boer 2019).
### German (2007) and US (2019) screening guidelines
(Heiligenhaus et al. 2007; Angeles-Han, Ringold, et al. 2019)

<table>
<thead>
<tr>
<th>ILAR category</th>
<th>ANA</th>
<th>Age at JIA onset (years)</th>
<th>JIA duration (years)</th>
<th>Recommended screening interval (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA, RF- PA, PsA, UA</td>
<td>+</td>
<td>≤6</td>
<td>≤4</td>
<td>3 months (German guidelines)</td>
</tr>
<tr>
<td>OA, RF- PA, PsA, UA</td>
<td>+</td>
<td>≤6</td>
<td>&gt;4</td>
<td>6 months (US guidelines)</td>
</tr>
<tr>
<td>OA, RF- PA, PsA, UA</td>
<td>+</td>
<td>≤6</td>
<td>&gt;7</td>
<td>12 months</td>
</tr>
<tr>
<td>OA, RF- PA, PsA, UA</td>
<td>+</td>
<td>&gt;6</td>
<td>≤2</td>
<td>6 months</td>
</tr>
<tr>
<td>OA, RF- PA, PsA, UA</td>
<td>+</td>
<td>&gt;6</td>
<td>&gt;2</td>
<td>12 months</td>
</tr>
<tr>
<td>OA, RF- PA, PsA, UA</td>
<td>-</td>
<td>≤6</td>
<td>≤4</td>
<td>6 months</td>
</tr>
<tr>
<td>OA, RF- PA, PsA, UA</td>
<td>-</td>
<td>≤6</td>
<td>&gt;4</td>
<td>12 months</td>
</tr>
<tr>
<td>OA, RF- PA, PsA, UA</td>
<td>-</td>
<td>&gt;6</td>
<td>n.a.</td>
<td>12 months</td>
</tr>
<tr>
<td>ERA, RF+ PA, SA</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>12 months</td>
</tr>
</tbody>
</table>

Screening for uveitis must be continued for at least seven years (German guidelines).

### UK guidelines (2006)
(Sen, Dick, and Ramanan 2015)

<table>
<thead>
<tr>
<th>ILAR category</th>
<th>ANA</th>
<th>Age at JIA onset (years)</th>
<th>Length of screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA, PsA, ERA</td>
<td>n.a.</td>
<td>&lt;3 years</td>
<td>8 years</td>
</tr>
<tr>
<td>OA, PsA, ERA</td>
<td>n.a.</td>
<td>3-4 years</td>
<td>6 years</td>
</tr>
<tr>
<td>OA, PsA, ERA</td>
<td>n.a.</td>
<td>5-8 years</td>
<td>3 years</td>
</tr>
<tr>
<td>OA, PsA, ERA</td>
<td>n.a.</td>
<td>9-10 years</td>
<td>1 year</td>
</tr>
<tr>
<td>RF- PA</td>
<td>+</td>
<td>&lt;6 years</td>
<td>5 years</td>
</tr>
<tr>
<td>RF- PA</td>
<td>+</td>
<td>6-9 years</td>
<td>2 years</td>
</tr>
<tr>
<td>RF- PA</td>
<td>-</td>
<td>&lt;7 years</td>
<td>5 years</td>
</tr>
<tr>
<td>OA, PsA, ERA, RF- PA</td>
<td>n.a.</td>
<td>&gt;11 years</td>
<td>1 year</td>
</tr>
</tbody>
</table>

Abbreviations: ANA, antinuclear antibodies; ERA, enthesitis-related arthritis; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis; OA, oligoarthritis; PA, polyarthritis; PsA, psoriatic arthritis; RF, rheumatoid factor; SA, systemic arthritis; UA, undifferentiated arthritis.

**Figure 2.1** Summary of guidelines for JIA-U screening
GENES AND BIOMARKERS

JIA is both a multifactorial and polygenetic disease, however, pathophysiology is still poorly understood (Vastert, Bhat, and Goldstein 2014). A variety of immune cell subtypes may play a role in the underlying mechanisms of JIA-U. While a comprehensive understanding of the changes in immune cells in JIA-U is lacking, previous studies have shown that patients show activated peripheral monocyte populations and altered frequencies of distinct functional T cell subsets (Walscheid et al. 2019; 2018). Accumulating evidence suggests that B cells play an important role in JIA-U. It is consistent with clinical findings that ANAs are a classical risk factor for JIA-U, as antibodies are produced by plasma cells (differentiated B cells) (Haasnoot, Kuiper, and de Boer 2019). In addition, small studies have revealed increased abundance of CD20+ B cells in eye tissues of cases with JIA-U (Kalinina Ayuso, van Dijk, and de Boer 2015; Kalinina Ayuso et al. 2014). Although rituximab, a monoclonal antibody targeting CD20 on B cells, is reported to be effective in small case series in treating refractory JIA-uveitis, it is not commonly used as treatment modality (Heiligenhaus et al. 2011). According to RNA-sequencing analysis of circulating B cells in JIA-U, memory B cell-associated gene circuits are involved and may contribute to the disease process (Wennink et al. 2020). Also, transcriptomic and proteomic analysis of iris tissue in JIA-U patients revealed increased expression for immunoglobulin genes and B cell-associated proteins (Wildschütz et al. 2019). Several case series presented histological and immunohistochemical reports of enucleated eyes and iridectomy specimens from patients with JIA-U in different stages of disease. These revealed an initial predominance of plasma cells (terminally differentiated B-cells) and significant numbers of CD20+ B cells (Haasnoot, Kuiper, and de Boer 2019).

The genetic predisposition for JIA-U involves genes that are implicated in immune pathways (Haasnoot, Kuiper, and de Boer 2019). The amino acid motif (YST) at position 10–12 in the HLA-DRB1 gene, encoding the beta subunit of HLA-DR, was found to be the primary association for uveitis susceptibility in girls in a genome-wide association study of >500 JIA cases with over four-year clinical follow-up (A.-M. J. W. Haasnoot et al. 2018). The YST motif appears also in alleles previously associated with JIA-U(Haasnoot et al. 2018; S. T. Angeles-Han et al. 2015; Wennink, de Boer, et al. 2021). This genetic marker for uveitis demonstrates sexual dimorphism that is conceptually consistent with the differences in clinical presentation between males and females; there is an apparent female predisposition to JIA-U, and the disease course in males is typically more complicated. According to the GWAS study, the YST motif was associated with uveitis in an unusually high proportion of girls. This makes it tempting to speculate that female patients without the YST motif have a very low
risk for uveitis. For confirmation that absence of YST is predictive of low risk in girls, a prospective study with ophthalmologic follow-up of at least four years is needed.

The YST-motif can be detected by polymerase chain reaction (PCR) using sequence-specific oligonucleotide probes. Additionally, TaqMan® SNP genotyping can be used, which uses the 5' nuclease activity of Taq polymerase to generate a fluorescent signal for single nucleotide polymorphisms (i.e., position 11 in HLA-DRB1), since the YST-motif shows strong linkage disequilibrium and commercial assays are available. However, next-generation sequencing is increasingly used for HLA typing and this method will type the variable exon sequences that encode the amino terminal domains that contain the YST-motif in great detail and allows also the detection of potentially relevant rare alleles that influence the function of this motif in the HLA-DR molecule.

In patients with JIA-U, serum autoantibodies directed against nuclear factors, such as histones, and chromatin are more common (Murray et al. 1997; Neuteboom et al. 1992). These autoantibodies have been shown to also bind ocular tissues (including iris/ciliary tissues), and may not be exclusively targeted against nuclear antigens (Walscheid et al. 2014). Other factors often found elevated in the blood of patients are acute phase proteins and innate stress mediators (Walscheid et al. 2015; van den Broek et al. 2015). In oligo- and polyarticular JIA-patients, elevated erythrocyte sedimentation rate is predictive for the risk for uveitis (Haasnoot et al. 2015). In addition, an increased level of the proinflammatory S100A12 (>250 ng/ml) at JIA-onset is associated with an increased risk for uveitis in JIA (Tappeiner et al. 2018).

**TREATMENT**

Managing JIA-U requires long-term treatment and a multidisciplinary approach, including collaboration between an ophthalmologist and pediatric immunologist. To prevent vision-threatening complications, the primary goal of treatment is to achieve stable remission as soon as possible. The recommended treatment target is to achieve zero cells in the anterior chamber in both eyes (SUN Criteria, anterior chamber cell grade equal to 0)(Bou et al. 2015; Leverette 1980). A variety of treatments have been explored over the years to control inflammation and preserve visual function. The goal of therapy should be to minimize the risk for complications caused both by inflammation itself and by topical corticosteroid use, which can have iatrogenic effects.

For JIA-U, topical corticosteroids have historically been the mainstay of treatment, but today it is only used as an initial treatment. The reason is that prolonged and
excessive use of topical corticosteroids may lead to severe adverse effects, including glaucoma, cataracts, and increased intraocular pressure (Clarke, Sen, and Ramanan 2016). As a rescue medication, short-term high dose systemic corticosteroids can be used. Note that peribulbar corticosteroid injections cause severe complications, including cataract and glaucoma development, and are not a standard treatment for these patients. Consequently, corticosteroids are not recommended for maintenance therapy in JIA-U, and the treatment transition in recent decades has been toward corticosteroid-sparing agents, which have proven to be valuable tools in lowering complications in retrospective studies (Wennink et al. 2022; Sen and Ramanan 2020).

Methotrexate (MTX) is a corticosteroid-sparing agent (also known as conventional disease-modifying antirheumatic drugs (cDMARDs)) and can be taken orally or subcutaneously, usually at a dose of 10-15 mg/m²/week (Giannini et al. 1992; Ruperto et al. 2004; Reiff et al. 1995). Folic or folinic acid supplementation is recommended to prevent MTX side effects (Shea et al. 2014). MTX has demonstrated efficacy in controlling ocular inflammation and reducing the need for corticosteroids in JIA-U. Based on a systematic review, approximately 70-75% of patients on MTX should see improvement in their disease severity (Simonini et al. 2013). Other cDMARDs can be used if MTX side effects presents as gastrointestinal complaints (or less frequently elevated liver enzymes, hair loss, mouth sores or rash) (Ferrara et al. 2018). In theory, MTX can be substituted with mycophenolate or azathioprine in these cases, but their efficacy varies more strongly (Doycheva et al. 2007; Goebel et al. 2011).

A “step-up approach” may be necessary when there is insufficient response to DMARDs or when uveitis severity is significant, particularly in young children with a complicated disease course. This step-up involves starting humanized monoclonal antibodies that inhibit cytokine signaling pathways, including inhibitors of tumor necrosis factor alpha (TNF-alpha) and interleukin-6 (IL-6)(Chen, Abiri, and Tsui 2021). According to positive results and safety profile from two international JIA-U trials (the SYCAMORE and the ADJUVITE trials), the anti-TNF-alpha agent adalimumab is considered to be a first choice biological agent for moderate-to-severe JIA-U (Quartier et al. 2018; Ramanan et al. 2014). Infliximab is the second most frequently used anti-TNF-alpha agent and may also be used to switch in cases that do not respond to adalimumab therapy. Collectively, the switch toward an alternative anti-TNF-alpha agent in these cases may improve disease management for about three quarters of patients (Gabriele Simonini, Druce, et al. 2014; Gabriele Simonini, Katie, et al. 2014). Testing for anti-adalimumab antibodies should be considered when JIA-U relapses under adalimumab therapy (Leinonen et al. 2017). The use of low dose MTX in combination of an anti-TNF-alpha agent may reduce the development of antibodies (Schmeling 2001). Recurrences of uveitis may also be caused by decreased efficacy or
decreased adherence due to the use of biosimilars. Side effects are more frequently described with the use of biosimilars, with pain at injection administration being the most common complaint (Kearsley-Fleet et al. 2023). Humanized monoclonal antibodies directed against the IL-6 receptor (tocilizumab) has been shown to be effective in JIA-U cases where anti-TNF-alpha therapy failed due to anti-drug antibodies (Angeles-Han, Ringold, et al. 2019b; Iannone et al. 2023; Ramanan et al. 2020). However, despite all the current treatment options, it is still challenging to achieve stable remission without corticosteroids in some children. For these cases, novel therapeutic approaches remain an unmet need. Inhibitors of Janus kinase (JAK), anti-CD20 B cell therapy, and anti-CTLA4 (abatacept) (Chen, Abiri, and Tsui 2021) are some promising approaches, but the current data is limited for JIA-U. As of now, adalimumab has the most favorable risk profile among biologics for pediatric uveitis, with an adverse event rate of 10.60 per patient year (most common are infections and infestations), and a low serious adverse event rate (0.29 per patient year) (Li et al. 2021).

**COMPLICATIONS**

Uveitis in children with JIA have a high risk for development of complications because the asymptomatic nature of this type of uveitis makes it prone to diagnostic delay and undertreatment (Heiligenhaus et al. 2019; Rypdal et al. 2021; Sen and Ramanan 2020) (Figure 2.2). Consequently, diagnosis relies heavily on intensive screening of JIA cases. Severe complications are present at first presentation in 20-45% of JIA-U patients (Heiligenhaus et al. 2013). The most frequent vision-threatening complication in JIA-U is cataract (Heiligenhaus et al. 2013; Cann et al. 2018; Thorne et al. 2007). The development of cataract might be related to prolonged treatment with topical corticosteroids (Thorne et al. 2010). Other frequent complications are band keratopathy (16–32%), glaucoma (8–19%) and posterior synechiae (25-29%). Less frequent complications are ocular hypotony (3-9%), cystoid macular edema (3-6%), optic disc swelling (3-4%) and epiretinal membrane formation (0-4%) (Heiligenhaus et al. 2013; Cann et al. 2018; Thorne et al. 2007).

By adulthood, approximately 30% of eyes become visually impaired (Haasnoot et al. 2016), with secondary glaucoma as the most common cause (de Boer, Wulffraat, and Rothova Br 2003).
In the past years, different studies identified several factors that are associated with a poor prognosis such as uveitis developing prior to arthritis in approximately 10–14% of patients, due to late detection (Paroli et al. 2003; Heiligenhaus et al. 2007). Similarly, Woreta et al. reported that active intraocular inflammation at presentation is a risk factor for at least one ocular complication at the initial visit (Woreta et al. 2007). In several studies, male patients were found to be associated with a complicated course (Edelsten et al. 2002; Zulian et al. 2002; Kalinina Ayuso et al. 2010) and an increased risk for cataract surgery, development of cystoid macula edema and papillitis (Kalinina Ayuso et al. 2010). Male sex has also shown to be an independent risk factor for poor visual prognosis in patients with JIA-U compared to girls (Kalinina Ayuso et al. 2010; Holland, Denove, and Yu 2009). Also, short interval between arthritis and uveitis diagnosis is reported as risk factor for uveitis in children with JIA (Rypdal et al. 2021; Zulian et al. 2002; Sabri et al. 2008; Chen, Roberton, and Hammerton 2004). In a recent multicenter, prospective cohort study in patients with JIA-U, 39% had one or more ocular complications attending the 18-year ophthalmology visit. Children with a shorter time interval between diagnosis of arthritis and uveitis had a higher risk for developing complications (Rypdal et al. 2021). In addition, uveitis at a younger age tend to have a greater risk for severe complications (BenEzra, Cohen, and Behar-Cohen 2007; Holland, Denove, and Yu 2009). In the study of Holland et al, age three years or younger at baseline was associated with the development of complications (Holland, Denove, and Yu 2009). Topical corticosteroid treatment in young children might lead to earlier development of cataract and glaucoma (Thorne et al. 2010; Sen, Dick, and Ramanan 2015). Lastly, severity of uveitis and complications at initial visit are prognostic factors for both later complications and vision loss (Woreta et al. 2007;
Uveitis associated with juvenile idiopathic arthritis

Gregory et al. 2013; Thorne et al. 2007; Holland, Denove, and Yu 2009; Heiligenhaus et al. 2007). Baseline cell grade >1+ cells have a high relative risk for development of new complications (Holland, Denove, and Yu 2009). The presence of >1+ anterior chamber flare at the initial visit was associated with 20/50 or worse and 20/200 or worse vision (Holland, Denove, and Yu 2009). Repeated laser flare photometry measurements may be of additional value. For example, a decrease in flare values by ≥50% of the initial value, 1 month after treatment intensification, is an early-stage prognostic factor for positive outcome (Orès et al. 2022; Davis et al. 2003). In addition, the objective measurements may also be useful for study purposes. For example, the previously mentioned ADJUVITE study used the anterior chamber flare values by the laser flare photometry as definition of active uveitis and as primary outcome (Quartier et al. 2018).

Early start with immunomodulatory therapy seems to be protective for the development of complications (Wennink et al. 2022; Gregory et al. 2013). The incidence of complications has decreased during the recent years, probably because of the improvement of the systemic treatment for JIA and JIA-U (Wennink et al. 2022; Cann et al. 2018). The start with MTX <1 year after onset of JIA-U postponed the development of cataract requiring surgery (Sijssens et al. 2007). The development of novel immunomodulatory treatments and early start, in combination with the standardized uveitis screening, might improve visual outcomes.

As mentioned earlier, cataract is the most common complication, causes reversible vision loss. All surgeries in JIA-U are challenging because of the young age and underlying inflammation. The uveitis must be completely controlled for ≥2 months with systemic immunomodulatory therapy (Magli et al. 2014; Foster and Rashid 2003; Bohnsack and Freedman 2013), in order to lower the risk of recurrence of uveitis, anterior capsule phimosis and cystoid macular oedema after cataract surgery. Before considering intraocular lens placement, risk factors such as age, refractory nature of JIA-U, presence of other complications and condition of the other eye need to be taken into account to optimize the long-term visual outcome (Sijssens et al. 2010; Yangzes et al. 2019; Mehta, Linton, and Kempen 2014).

Secondary glaucoma
Secondary glaucoma is one of the most serious and potentially blinding complications in pediatric uveitis (de Boer, Wulffraat, and Rothova Br 2003; Sijssens et al. 2006). Based on a retrospective analysis in a tertiary care referral center, secondary glaucoma developed in 26% of the children with uveitis (Sijssens et al. 2006), with glaucoma
developing most frequently in non-infectious uveitis (20% in JIA-U and 28% in idiopathic anterior uveitis (Sijssens et al. 2006; Kouwenberg et al. 2022).

Uveitic glaucoma develops as a result of increased resistance to the aqueous humor outflow by several mechanisms, including mechanical obstruction due to entrapment of inflammatory cells and debris in the trabecular meshwork, swelling of the meshwork itself, and secondary scarring or collapse of the trabecular meshwork and/or Schlemm’s canal. Also, treatment with corticosteroids may increase outflow resistance by modifying the trabecular meshwork (Kaur, Kaushik, and Singh Pandav 2013). The proportion of eyes with elevated intraocular pressure (IOP) and glaucoma increases during the first 5 years after the uveitis diagnosis. After 5 years, the incidence of glaucoma remained stable (Sijssens et al. 2006). Regular IOP evaluation for a longer period of time is mandatory for early detection of an IOP increase, taking into account the risk profile for developing uveitic glaucoma (Sabri et al. 2008). In JIA-U, ANA positivity, anterior segment complications (cataract, band keratopathy and/or posterior synechiae) at diagnosis, IOP >21 mmHg during the first uveitis remission and a higher amount of topical corticosteroids use are associated with an increased risk for glaucoma surgery. In addition, the necessity of using three types of IOP-lowering medication indicates a high risk for glaucoma surgery, as in a retrospective study the majority (68%) of eyes had glaucoma surgery within one year of starting a third type of medication (van Meerwijk et al. 2023).

With the introduction of Icare rebound tonometry, the IOP can be measured in young children during the normal clinical exam (Flemmons et al. 2011). Additional evaluation is difficult in children, whereas visual field tests do not provide reliable responses in younger children. An optical coherence tomography (OCT) could evaluate the retinal nerve fiber layer and/or the macular ganglion cell layer, however, no normative database for children is available. Moreover, aspects such as optic disc swelling due to papillitis, epiretinal membrane and dense vitreous opacities may distort the results, making OCT scans difficult to interpret. Repeatedly performing OCT scans per patient could provide useful information on changes in the optic disc over time.

The first step in case of ocular hypertension is pharmacologically lowering the IOP and minimizing topical corticosteroids (Figure 2.3). In 30-61% of the children with uveitic glaucoma, a surgical intervention is mandatory (Gautam Seth et al. 2018; Merayo-Lloves et al. 1999; Heinz et al. 2009). Based on recent research, the advice is to start with a goniotomy as a first intervention (Iannucci et al. 2023; van Meerwijk et al. 2023), because of the relative simplicity of the procedure, its high success rate and low risk profile. When peripheral anterior synechiae are present, especially in the area
to be treated, or failure develops, it is advisable to use a glaucoma drainage implant (GDI) (most well-known devices are Baerveldt GDI and Ahmed GDI) (Figure 2.3). GDI’s adequately reduce the IOP, but their complication profile is a relative disadvantage, with severe IOP fluctuations, bleb and tube problems in the long term (Zhou et al. 2015; Kalinina Ayuso, Scheerlinck, and de Boer 2013). The use of a trabeculectomy or cyclodiode laser is less advisable in JIA-U, due to a relatively high amount of re-interventions needed after the primary surgery (Wiese, Heiligenhaus, and Heinz 2014; Heinz, Koch, and Heiligenhaus 2006).

**Step-by-step: Management for pediatric uveitic glaucoma**

<table>
<thead>
<tr>
<th>Measurement IOP and evaluation optic nerve on regular basis from start uveitis diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of topical steroids, while providing adequate uveitis control with systemic immunosuppressive medications</td>
</tr>
<tr>
<td>Start IOP-lowering medication</td>
</tr>
<tr>
<td>When starting triple therapy*: referral to glaucoma specialist</td>
</tr>
<tr>
<td>Goniotomy procedure when no significant peripheral anterior synechiae OR Glaucoma drainage implant (Baerveldt or Ahmed implant)</td>
</tr>
<tr>
<td>Glaucoma drainage implant (Baerveldt or Ahmed implant)</td>
</tr>
</tbody>
</table>

**Figure 2.3** Step-by-step approach of the management of uveitic glaucoma in JIA-Uveitis. 
*The use of three different types of intraocular pressure (IOP)-lowering medication
IDIOPATHIC CHRONIC ANTERIOR UVEITIS AND JIA-U: THE SAME DISEASE?

Idiopathic chronic anterior uveitis (iCAU) is a subgroup of pediatric uveitis patients that shows similarities with JIA-U. ICAU accounts for approximately 30-40% of the children with anterior uveitis, and cannot be distinguished clinically from JIA-U, based on ophthalmological characteristics (Holland, Denove, and Yu 2009; Tugal-Tutkun 2011; Ferrara et al. 2019). In contrast with JIA-U, no routine ophthalmologic screening for uveitis occurs in iCAU patients, resulting in more vision-threatening ocular complications compared to JIA-U because of late detection. However, long-term visual outcome is similar between the two groups when adequately treated with immunomodulatory therapy (Kouwenberg et al. 2022). Especially ANA-seropositive iCAU shows similarities with JIA-U with regards to uveitis characteristics, clinical course, and response to systemic treatment (Heiligenhaus et al. 2020). Therefore, it is not surprising that recent therapy guidelines and the Childhood Arthritis and Rheumatology Research Alliance recommend that JIA-U and iCAU should be treated in a similar manner (Heiligenhaus et al. 2019; Angeles-Han, Lo, et al. 2019; Foeldvari et al. 2023; Solebo et al. 2020).

Furthermore, the finding of shared genetic risk alleles for both JIA-U and iCAU (HLA-DQB1*04:02 and HLA-DRB1*08:01), leads to the hypothesis that iCAU is identical to JIA-U without arthritis (Wennink, de Boer, et al. 2021). While iCAU could be a first manifestation of cases that later develop JIA, only a minority of the patients with an onset of anterior uveitis will develop arthritis at a later stage (Wennink et al. 2021; Heiligenhaus et al. 2020; Kalinina Ayuso et al. 2010). However, the development of arthritis might be suppressed due to the common use of immunomodulatory therapy in JIA. Haasnoot et al. revealed that iCAU could not be distinguished from JIA-U by comparison of multi-cytokine profiles in aqueous humor (Haasnoot et al. 2016), which was consistent with the observation of previous studies (Kalinina Ayuso et al. 2013; Kalinina Ayuso, van Dijk, and de Boer 2015; Walscheid et al. 2015). Since the collection of aqueous humor is invasive and not preferable in children, Angeles-Han et al. studied proteomics in tears (Angeles-Han et al. 2018). They discovered 29 differentially expressed proteins in a small cohort of children with JIA-U and iCAU that were involved in the extracellular exosomes. These proteins may provide clues to intrinsic differences between JIA-U and iCAU, despite their similar clinical phenotypes and shared genetic alleles. Investigation of serum of pediatric uveitis patients suggests however common immune activity, regulatory processes and a common adaptive disease mechanism for both disease entities (Walscheid et al. 2015; 2019).
DISCUSSION AND CONCLUSION

Over the past decade, new insights have been gained into the pathogenesis, risk factors, and treatment strategies of JIA-U. In particular, adalimumab treatment in addition to MTX has resulted in better visual prognosis with fewer structural complications (Ramanan et al. 2017; Wennink et al. 2022). Due to the risks for cataract and glaucoma, topical corticosteroids are no longer recommended for the maintenance treatment of JIA-U. The use of other biologicals, such as tocilizumab, has also been proven effective in cases refractory to anti-TNFα therapy. Several studies have shown that inflammation control is directly related to visual outcome (Gregory et al. 2013). Despite this, there are still patients who are refractory to biological therapy, or who developed antibodies against it.

Despite progress regarding the immunopathogenesis of JIA, many questions remain unanswered. A major question is whether biomarkers can predict patient response to treatment. Through the use of these biomarkers, early remission could be achieved with fewer side effects from multiple treatment strategies and biomarkers may aid in the prediction of uveitis in JIA patients. Predicting more accurately which patients are not at risk would reduce the need for prolonged and frequent screenings by eye specialists. A reduction in hospital visits and burden on families would result from this.

Although progress has been made regarding JIA-U treatment and pathogenesis in the last decade, complications remain prevalent, with secondary glaucoma being the most common cause of visual loss, despite intensive immunomodulatory therapy. To estimate the risk of developing complications during follow-up, laser flare photometry can be valuable (Davis et al. 2003). Thus, prolonged inflammation and topical corticosteroid therapy should be avoided as much as possible to prevent structural damage. It is important to treat these patients with a multidisciplinary team of ophthalmologists and pediatric rheumatologists.