Juvenile idiopathic arthritis and associated uveitis: A review of pathogenesis, diagnosis, and management

Costanza Barresi[1,2], Francesco Baldo[3], Matteo Menean[1,2], Achille Marino[3], Stefania Costi[3], Cecilia B. Chighizola[3,4], Roberto F. Caporali[3,4,5], Elisabetta Miserocchi[1,2]

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Abstract:

Juvenile idiopathic arthritis (JIA) is the most common rheumatologic disorder in children, posing significant physical and emotional challenges due to its chronic nature and the need for prolonged immunosuppressive therapies. Uveitis is the most common extra-articular manifestation of JIA, and it can be a sight-threatening condition. Despite advances in biologic treatments, JIA continues to present substantial therapeutic challenges, necessitating multiple treatment attempts and close monitoring for secondary failures. JIA-associated uveitis remains one of the most challenging and aggressive types of uveitis, particularly in children, due to its early onset, chronicity, and limited therapeutic responses despite new treatments. Early recognition and prompt treatment of both arthritis and uveitis are essential for achieving sustained remission and preventing complications. Effective management of JIA-uveitis requires a collaborative approach between pediatric rheumatologists and ophthalmologists to ensure timely assessments, regular screenings, and necessary therapy adjustments. This integrated care approach is crucial for achieving optimal outcomes. Therefore, this review aims to extensively analyze the pathogenesis, diagnosis, and therapy of JIA and its associated uveitis.

Keywords:

Diagnosis, juvenile idiopathic arthritis, therapy, uveitis

Introduction

Juvenile idiopathic arthritis (JIA) is the most prevalent rheumatologic disorder in children, imposing a significant burden on affected individuals due to its chronic nature. This disease can severely impact both the physical and emotional well-being of children, as well as their daily activities, compounded by the necessity for prolonged, sometimes poorly tolerated immunosuppressive therapies. Enhanced understanding of the disease mechanisms and the advent of biologic therapies since 2000 have markedly altered the disease's natural progression, significantly reducing the incidence of permanent joint damage and visual impairment caused by uveitis and steroid-related toxicity.[1]

Despite these advancements, managing patients with JIA, especially those with concomitant uveitis, remains challenging due to refractory disease forms, drug side effects, and poor adherence to therapy, particularly among adolescents. Early recognition and prompt treatment of both arthritis and uveitis are crucial to achieve sustained remission and preventing complications.

This review does not address systemic arthritis, as it is increasingly considered part of the autoinflammatory disorder spectrum necessitating treatments (like anti-IL-1 drugs) that differ significantly from those used for other JIA categories, and it is not associated with the development of uveitis.

Juvenile Idiopathic Arthritis

Overview on epidemiology and pathogenesis

The prevalence of all forms of JIA is estimated to range from 16 to 150 per 100,000, with an incidence varying between 5.3 per 100,000[2] and 19.6 per 100,000.[3] These rates can differ based

[1]Department of Ophthalmology IRCCS San Raffaele Scientific Institute, [2]Department of Ophthalmology, Vita-Salute San Raffaele University, [3]Department of Pediatric Rheumatology, Unit of Pediatric Rheumatology, ASST G. Pini-CTO, [4]Department of Clinical Sciences and Community Health, University of Milan, [5]Department of Rheumatology and Medical Sciences, ASST G. Pini-CTO, Milan, Italy

Address for correspondence: Prof. Elisabetta Miserocchi, Department of Ophthalmology, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, Milan, 20132, Italy. E-mail: miserocchi.elisabetta@gmail.com

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on geographic and ethnic backgrounds. A recent study found that the incidence of JIA was highest among individuals of White ethnicity (6.2 per 100,000) compared to those of mixed (3.0 per 100,000), Asian (2.7 per 100,000), and Black (2.9 per 100,000) ethnic groups.[4,5]

JIA is more prevalent in females, with an overall male-to-female (M/F) ratio ranging from 1:2 to 1:3.[6] Notably, specific subtypes exhibit even greater gender disparities; for instance, oligoarticular disease complicated by anterior uveitis is significantly more common in females (M: F 1:8).[6] Conversely, enthesitis-related arthritis (ERA) is more prevalent in boys.[7] There is little to no sex difference observed in systemic JIA. The age of onset also varies across different JIA forms and between genders.

The pathogenesis and etiology of JIA are complex and remain incompletely understood. As with most autoimmune disorders, interactions among genetic factors, immune mechanisms, and environmental exposures are believed to contribute significantly in most cases.[8]

Classification

The most widely used classification for JIA is the International League Against Rheumatism (ILAR) classification. According to these criteria, JIA is defined by the presence of arthritic features in children under 16 years of age with at least 6 weeks of active symptoms in the absence of other medical causes. JIA is further categorized based on the number of involved joints, the presence or absence of rheumatoid factor (RF) and antinuclear antibodies (ANA), and the presence of enthesitis and/or psoriasis, resulting in seven distinct categories [Table 1].[9] However, this classification system has some weaknesses, such as using the number of involved joints as a classification criterion rather than as an expression of disease severity and prioritizing the number over the distribution of affected joints. In addition, it treats ERA and juvenile psoriatic arthritis as separate entities despite the central role of enthesitis in both forms. The ILAR criteria also involve a complex network of interrelated criteria, which can lead to misclassification (e.g., a patient with systemic JIA should not have first-degree relatives with psoriasis).[10]

To address these flaws, PRINTO has proposed a new classification system based on clinical and laboratory homogeneity. The provisional classification recognizes five categories of arthritis: enthesitis/spondylitis-related, early-onset ANA positive, RF positive, systemic, and other. However, this preliminary effort does not cover psoriatic arthritis, which would be categorized among the "other" subgroups. This system distinguishes between forms that resemble adult counterparts and early-onset ANA-positive arthritis, which appears specific to the pediatric population and carries the highest risk of developing chronic anterior uveitis (CAU).[11]

Oligoarthritis

It is the most common subtype of JIA, predominantly affecting young girls below 6 years of age. Clinically, it is characterized by asymmetric involvement of large joints and an increased risk of asymptomatic anterior uveitis, especially in ANA-positive patients.[8]

Table 1: Classification criteria for juvenile idiopathic arthritis (International League Against Rheumatism 2001)

Type	Manifestations
Polyarthritis	Five or more joints during the first 6 months
	Subtypes
	RF negative polyarthritis
	RF-positive polyarthritis: Two or more tests for RF at least 6 months apart during the first 6 months of disease are positive
ERA	Arthritis and enthesitis OR arthritis or enthesitis with two or more between
	SIJ tenderness and/or inflammatory lumbosacral pain
	HLA-B27, male sex and onset of arthritis >6 years of age
	Family history ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease, reactive arthritis, acute anterior uveitis in a first-degree relative
	Acute symptomatic anterior uveitis
JPsA	Arthritis and psoriasis OR arthritis with at least two of the following items
	Dactylitis
	Nail pits or onycholysis
	Family history of psoriasis in a first-degree relative
Exclusion criteria	Psoriasis in the patient or a family history of psoriasis in a first-degree relative (not for JPsA)
	Male sex, HLA-B27 positivity and arthritis beginning >6 years of age (not for ERA)
	Ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease, reactive arthritis, acute symptomatic anterior uveitis, or a history of one of these disorders in a first-degree relative (not for ERA)
	The presence of IgM RF on at least two occasions 3 or more months apart (not for RF-positive poliarthritis)
	The presence of systemic arthritis
	Arthritis fulfilling two or more JIA categories

JPsA: Juvenile psoriatic arthritis, ERA: Enthesitis-related arthritis, RF: Rheumatoid factor, SIJ: Sacroiliac joints, IgM: Immunoglobulin M, JIA: Juvenile idiopathic arthritis

Polyarthritis

It is defined by the involvement of five or more joints within the first 6 months of disease onset. RF-positive polyarthritis is closely related to adult rheumatoid arthritis, typically featuring symmetric involvement of the small joints of the hands and feet, often alongside large joints. This form can show an aggressive disease course, characterized by early joint erosion and damage if untreated. RF-negative polyarthritis presents a more heterogeneous phenotype, with some forms resembling aggressive ANA-positive oligoarthritis and other less categorizable forms.[8]

Enthesitis-related arthritis and psoriatic arthritis

ERA is most common in boys over the age of 6 and is named for its prevalent clinical feature, enthesitis (inflammation at the tendon-bone insertion), along with axial involvement, predominantly in the sacroiliac joints (SIJ). It is associated with HLA-B27 and an increased risk of acute, symptomatic anterior uveitis. ERA belongs to the broad group of juvenile

spondyloarthropathies and can be diagnosed if both arthritis and enthesitis are present or if either is present along with at least two of the following: male sex above 6 years, inflammatory back pain, acute symptomatic anterior uveitis, HLA-B27 positivity, SIJ tenderness, or a first-degree relative with spondyloarthropathy. In the new classification, the nomenclature will change to ERA/spondylitis-related arthritis.[11] Psoriatic arthritis appears to encompass at least two distinct categories of patients. One group shows similarities with early-onset ANA-positive arthritis, involving small joints, dactylitis, and an aggressive disease course. The other group has features resembling adult psoriatic arthritis and is part of the spondyloarthropathy spectrum.[12]

Diagnostic workup

Clinical evaluation plays a pivotal role in comprehensively assessing children with arthritis. During history taking, it is essential to explore family history, particularly regarding autoimmune diseases such as arthritis, spondyloarthritis, psoriasis, and thyroid disorders. Red flags including fevers, night sweats, and weight loss should prompt clinicians to consider malignancies and infections.[13]

Examination should include careful general examination with inspection also for skin lesions, lymphadenopathy, and mucosal lesions. Joint assessment should involve a functional analysis of body movement. Crucially, joints such as the cervical spine, temporomandibular joint, and SIJ may be affected and require thorough clinical evaluation. If clinical suspicion of involvement of one of these joints arises, magnetic resonance imaging (MRI) is the preferred imaging modality.[14]

Despite the evolution of diagnostic techniques, so far, no test is confirmative of the diagnosis of JIA, which still relies on the exclusion of other causes of arthritis. The diagnostic workup must be comprehensive as various conditions can present with arthritis-like symptoms. In cases of monoarthritis and oligoarthritis, infection and malignancy must be excluded. X-rays of the affected joint and, if necessary, MRI can aid in ruling out bone lesions, septic arthritis, and osteomyelitis.[13] Musculoskeletal ultrasound is increasingly utilized in JIA due to its superior sensitivity in detecting subclinical synovitis, making it a valuable, easily accessible, nonirradiating tool throughout JIA management, aiding in diagnostic characterization, subtype classification, procedural guidance, and therapeutic decision-making during follow-up (FU).[15] Blood tests including full blood count, blood film, and lactate dehydrogenase levels can assist in the differential diagnosis, particularly with hematological malignancies. In cases of monoarthritis, septic arthritis and tuberculosis should always be ruled out.[13]

Overview of juvenile idiopathic arthritis treatment

Treatment principles for nonsystemic JIA can be drawn from the 2019 and 2021 ACR guidelines.[16,17]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used early on to alleviate pain and joint stiffness and are recommended in oligoarthritis, sacroiliitis, enthesitis, and, in conjunction with other treatments, polyarthritis. Commonly used NSAIDs include naproxen and ibuprofen. Intra-articular joint injections (IACI) are a potent means to ensure prompt symptom remission by minimizing systemic exposure to steroids. Triamcinolone hexacetonide is the drug of choice for its long-lasting effect, with a common practice of avoiding repeating joint injections more than three times a year.[18]

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) should be initiated in oligoarthritis if arthritis persists despite NSAIDs and IACI and in all cases of polyarthritis.

Methotrexate (MTX) remains a cornerstone of arthritis treatment. Optimal dosing of MTX in JIA is achieved with parenteral administration of 10–15 mg/m^2/week, with no additional therapeutic benefit associated with further dosage increases. MTX should be administered for up to 9–12 months to appreciate its full therapeutic effect.[19]

Biologic disease-modifying antirheumatic drugs DMARDs (bDMARDs) are recommended after failure of at least one csDMARD in oligoarthritis. Tumor necrosis factor (TNF) alpha inhibitors, such as etanercept (ETN) (in patients without uveitis) or adalimumab (ADA), are usually the drugs of choice. It is notable that, except for NSAIDs, no drug has been officially approved for oligoarthritis.[20]

Polyarthritis should receive treatment with MTX immediately after diagnosis, with early initiation of a bDMARD considered in those with involvement of high-risk joints or clinical features of an aggressive disease.[21]

Several bDMARDs, including TNF alpha inhibitors (etanercept, ADA, and golimumab), IL-6 inhibitors (tocilizumab [TOC]), and a CTLA4 co-stimulation inhibitor (abatacept), have been approved for poly JIA [Table 2]. Other bDMARDs, such as infliximab (INF) (TNF inhibitor) and rituximab (a CD20 monoclonal antibody), are used, off-label, to treat refractory polyarticular JIA.[20,22]

A relatively new class of drugs, Janus Kinase Inhibitors (JAKi), has shown promising results for the treatment of refractory disease. Tofacitinib was approved for poly JIA in 2020, while baricitinib and upadacitinib are currently under investigation.[20]

Regarding ERA, the 2019 ACR suggests treatment based on the number of affected joints following polyarticular or oligoarticular disease. However, hip involvement and sacroiliitis are risk factors for poor outcomes and must be considered for the early start of bDMARDs. First-line biologic is usually a TNF inhibitor, with etanercept being the most widely used and showing good effectiveness;[23] however, due to the prominent role of the IL17–IL23 axis in this disease, a rising role for drugs addressing these specific molecules such as secukinumab and ixekizumab is seen;[24] NCT04527380) JAKi also shows promising preliminary results in ERA patients.[25]

Table 2: Biologic medication currently used in juvenile idiopathic arthritis-associated uveitis treatment

Medication	Dose (maximum dose)	Route
INF	For children ≥4 years of age and adolescents: 5–20 mg/kg every 4–8 weeks afte r loading doses at 0, 2, and 6 weeks (1000 mg, maximum rate of 125 mL/h)	Intravenous
ADA	Fixed dosing for children ≥2 years of age <15 kg: 10 mg every 2 weeks; 15–30 kg: 20 mg every 2 weeks; ≥30 kg: 40 mg every 2 weeks; alternative dosing from 2 to <4 years of age: 24 mg/m^2/dose every 2 weeks; 15–30 kg: 20 mg every 2 weeks; ≥30 kg: 40 mg every 2 weeks (20 mg/dose) alternative dosing from 4 to 17 years of age: 24 mg/m^2/dose every 2 weeks (40 mg/dose)	Subcutaneous
Golimumab	Standard dose of 50 mg every 4 weeks in patients weighing ≥40 kg and 30 mg/m^2 body surface area in patients weighing ≤40 kg	Subcutaneous
Abatacept	For ≥6 years of age with polyarticular JIA: <75 kg: 10 mg/kg at 0, 2, and 4 weeks, then every 4 weeks; 75–100 kg: 750 mg at 0, 2, and 4 weeks, then every 4 weeks; >100 kg: 1000 mg at 0, 2, and 4 weeks, then every 4 weeks (1000 mg/dose)	Intravenous
	For ≥2 years of age with juvenile polyarticular or JPsA: 10–25 kg: 50 mg weekly; 25–50 kg: 87.5 mg weekly; ≥50 kg: 125 mg weekly (maximum dose as specified)	Subcutaneous
TOC	For ≥2 years of age: <30 kg: 10 mg/kg every 4 weeks; ≥30 kg: 8 mg/kg every 4 weeks (maximum dose 800 mg)	Intravenous
	For ≥2 years of age: <30 kg: 162 mg every 3 weeks; ≥30 kg: 162 mg every 2 weeks (162 mg/dose)	Subcutaneous
Tofacitinib	For children ≥2 years of age and adolescents: 10–20 kg: 3.2 mg twice daily (oral solution); 20–40 kg: 4 mg twice daily (oral solution); ≥40 kg: 5 mwg twice daily (tablet or oral solution)	Oral

JPsA: Juvenile psoriatic arthritis, JIA: Juvenile idiopathic arthritis, ADA: Adalimumab, INF: Infliximab, TOC: Tocilizumab

Juvenile Idiopathic Arthritis-Associated Uveitis

Epidemiology and risk factors

Uveitis is the most frequent and severe extra-articular complication of JIA, possibly leading to permanent vision loss if left untreated. Despite being the leading cause of pediatric uveitis in most series, the frequency of JIA-associated uveitis (JIA-U) varies widely.[26] The reported prevalence of uveitis among patients with JIA, ranges from 11.6% to 30%, being higher in Northern (19.1%) and Southern Europe (18.8%), and lower in Latin America (6.4%), Africa, Middle East (6%), and Southeast Asia (5%).[27] The differences reported between geographical regions may reflect non only genetic and environmental factors, but also significant discrepancies in the availability of ophthalmological screening across countries. Furthermore, uveitis prevalence varies considerably between different subtypes of JIA, being mostly absent in patients with systemic arthritis but affecting up to half of those with oligoarthritis in some cohort studies.[28] As a result, three out of four JIA patients with uveitis present oligoarthritis. Further established risk factors for the occurrence of JIA-U are very young age at onset of arthritis (<6 years old), ANA-positivity status, and female sex.[27,29] HLA-DRB1*11 and *13 loci have been associated with a more common occurrence of uveitis in JIA.[30]

Uveitis in JIA patients is more frequently bilateral (in about 75% of cases) and occurs most likely in the first 4 years after the onset of arthritis, despite cases being reported even after 10 years after arthritis. JIA is commonly diagnosed before the onset of uveitis. However, in approximately 10% of cases, children are first diagnosed with uveitis, with the diagnosis of JIA occurring later.[26] Differential diagnosis should include all the causes of intraocular inflammation in the pediatric population (infectious, noninfectious, and neoplastic). Analyzing a patient's medical history, conducting thorough laboratory assessments, and examining the characteristics of uveitis are crucial steps in identifying its underlying etiology.[31,32]

Clinical manifestations and diagnosis

The most common form of JIA-U is chronic recurrent nongranulomatous anterior uveitis, which is often asymptomatic in the early stages of the disease.[9]

Typically, the eye in JIA-U is white being totally asymptomatic despite high grade of intraocular inflammation. The uninflamed "white eye" is the mainstay of this particular subset of uveitis in children population.

Uveitis usually occurs bilaterally, involving simultaneously both eyes or starting unilaterally and involving subsequentially the fellow eye. However, in about 25%, the uveitis presents unilaterally. During active uveitis, a mild-to-moderate degree of fine anterior chamber cells is present, variably associated with nongranulomatous keratic precipitates of fine endothelial inflammatory deposits. Occasionally, active JIA-uveitis can present granulomatous keratic precipitates and posterior segment involvement.[33] Secondary posterior inflammatory involvement may be observed, especially in chronic untreated cases.

Despite recurrent anterior uveitis being the most common form of uveitis associated with JIA, the landscape of JIA-U is extremely heterogeneous, displaying distinct characteristics and risks across different JIA subsets [Table 3]. Specifically, acute anterior uveitis has been more commonly reported in patients presenting specific subsets of JIA, characterized by HLA-B27 positivity (ERA).[34-37] These patients present an acute onset of anterior uveitis with painful red eyes, photophobia, and moderate-to-severe anterior chamber inflammation.

Children complain about visual symptoms only in the late stages of the disease when the posterior segment is involved with vitritis or macular edema as a result of chronic asymptomatic uveitis. As a matter of fact, diagnosis mainly relies on regular screening programs, essential for detecting and treating CAU at an early stage and preventing sight-threatening complications.[38-40] The American College of

Rheumatology/Arthritis Foundation issued in 2019 the recommendations for the screening, monitoring, and treatment of uveitis in children with JIA.[41] These guidelines emphasize regular ophthalmic assessment, including visual acuity testing, slit-lamp examination, intraocular pressure measurement, and dilated fundus examination. High-risk children, such as those with oligoarticular and RF-negative polyarticular JIA, positive ANA test, younger than 7 years of age at JIA onset, or JIA duration of 4 years or less, should undergo ophthalmic screening every 3 months.[42] Children at low-to-moderate risk may be evaluated less frequently, every 6–12 months.[43] In addition, the British Society for Pediatric and Adolescent Rheumatology suggests bimonthly screening for 6 months after tapering or stopping immunosuppressive medications for arthritis treatment.[38,40]

Complications

The asymptomatic nature of JIA uveitis carries potential risks of diagnostic delay and undertreatment, which consequently leads to a high rate of complications.

Band keratopathy occurs in 16%–32% of JIA uveitis cases and represents a common complication that can lead to impaired vision and amblyopia [Figure 1].[44] It is the result of calcium deposition at the level of the corneal epithelial basement membrane and Bowman's membrane due to chronic inflammation. The most effective treatment approach is chemical chelation with ethylenediaminetetraacetic acid.[45]

Severe complications could be observed at first presentation in 20%–45% of JIA patients with uveitis, with cataract formation being the most frequent vision-threatening complication.[44,46] The development of cataracts in children with uveitis may be associated with prolonged use of topical corticosteroids, ongoing active uveitis (>0.5+ cells in the anterior chamber), and the presence of posterior synechiae as a marker of long-standing inflammation [Figure 2].[44,47] Cataract surgery in these patients poses significant challenges, primarily due to the presence of posterior synechiae and pupillary membranes that may complicate the surgical procedure. In addition, there is a risk of postoperative complications including hypotony, intraocular lens (IOL) deposits, macular edema, and cyclitic or fibrous membrane formation.[47,48] To minimize the risk of postsurgical complications, most uveitis specialists suggest controlling inflammation for at least 3 months before surgery.[31] The surgical approaches used in children with JIA uveitis may vary and depend on the degree or activity of inflammation. Concerns about the potential formation of inflammatory membranes on the IOL in children with uveitis

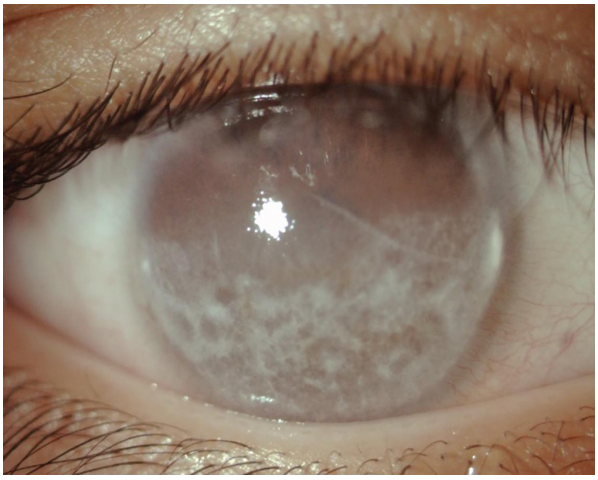

Figure 1: Diffuse band keratopathy in a patient with undertreated juvenile idiopathic arthritis

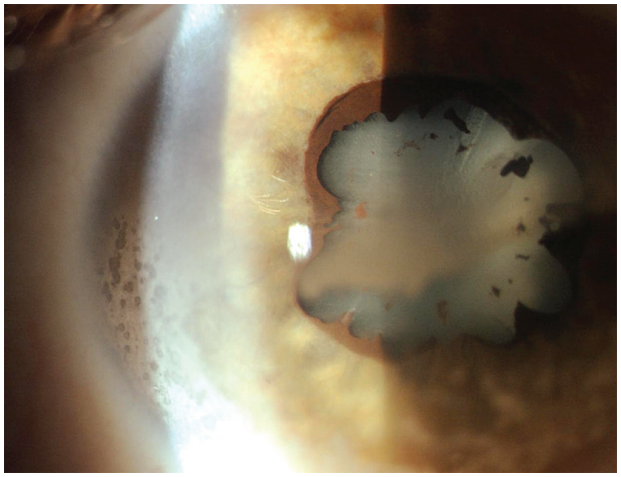

Figure 2: Development of posterior synechiae, cataract, and early band keratopathy in a patient with chronic juvenile idiopathic arthritis-associated uveitis

Table 3: Uveitis characteristics among different subsets of juvenile idiopathic arthritis

	Rate of uveitis (%)	Female:male ratio	Characteristics
Polyarthritis			
Wirth negative RF	10–20	3:1	Onset in early childhood. Chronic, often asymtpomatic
With positive RF	<5	4:1	Onset in early childhood. Chronic, often asymtpomatic
Systemic arthritis	<5	1:1	Onset in early childhood. Chronic, often asymtpomatic
Oligoarthritis			
Persistent	10–20	3:1	Onset in early childhood. Chronic, often asymtpomatic
Extended	20–40	3:1	Onset in early childhood. Chronic, often asymtpomatic or acute, with red eye and symptomatic
ERA	10–20	1:4	School age. Acute, often symtpomatic
Psoriasic arthritis	5–20	2:1	Variable onset (20% in school age). Chronic, often asymtpomatic

RF: Rheumatoid factor, ERA: Enthesitis-related arthritis

have dissuaded many ophthalmologists from IOL implantation during cataract extraction.[48,49] Historically, aphakia has been considered a preferable option for bilateral cataracts, whereas IOL implantation is more feasible for unilateral cataracts. However, managing aphakic eyes with spectacles or contact lenses and implementing occlusion therapy is fundamental to prevent amblyopia.

Glaucoma is another common complication of chronic uveitis in JIA patients. The prevalence of glaucoma ranges from 14% to 42%, which is notably higher compared to other forms of uveitis.[44] There is a suggestion that JIA itself acts as an independent risk factor for developing glaucoma. Uveitic glaucoma arises due to increased resistance to the outflow of aqueous humor due to mechanical obstruction of inflammatory cells and debris in the trabecular meshwork, swelling, and secondary scarring of the trabecular meshwork and/or the Schlemm's canal.[50] In addition, corticosteroid treatment may contribute to increase outflow resistance by altering the trabecular meshwork. Managing glaucoma in JIA-U poses significant challenges since medical treatment is often ineffective.[51] Surgical intervention becomes necessary in 30%–61% of cases, with recent research suggesting goniotomy as the first surgical intervention due to its relative simplicity, high success rate, and low risk profile.[52] However, if peripheral anterior synechiae are present or if initial treatments fail, is advisable to use a glaucoma drainage implant (GDI) such as Baerveldt GDI or Ahmed GDI [Figure 3].[51,53] Trabeculectomy or cyclodiode laser treatment are less recommended in JIA-U due to the relatively high number of re-interventions after the primary surgery.

Less frequent complications include ocular hypotony (3%–9%), cystoid macular edema (3%–6%), optic disc swelling (3%–4%), and epiretinal membrane formation (1%–4%).[34,37,54]

Treatment

Managing JIA-U requires a multidisciplinary approach, with the collaboration of trained uveitis experts and pediatric rheumatology specialists with the aim to prevent vision-threatening complications and achieve stable remission as soon as possible.[38] As a result, treatment often involves a combination of topical, local, and systemic therapies.[37,54] The recommended treatment target is to achieve zero cells in the anterior chamber in both eyes (SUN Criteria, anterior chamber cell grade 0).[55]

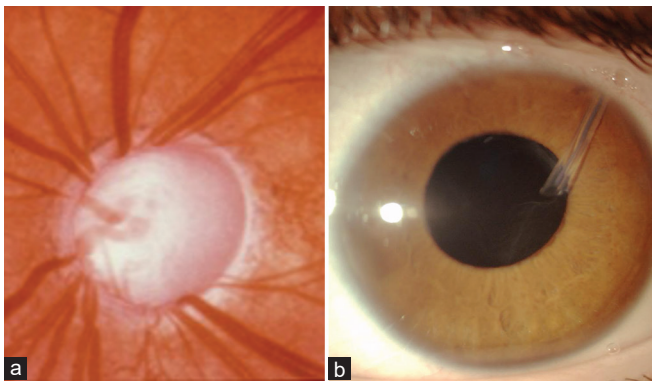

Figure 3: (a) Optic disc excavation in uvenile idiopathic arthritis-associated uveitis (JIA-U). (b) Baerveldt valve in a patient with JIA-U-associated glaucoma

Local treatment

Topical corticosteroids should be used as first-line treatment to control inflammation and should be tapered until the anterior chamber cellular reaction comes under control. To prevent the formation of posterior synechiae, cycloplegics eye drops, including tropicamide and cyclopentolate, are warranted in association with topical steroids.[43] If topical steroids fail to control the inflammation, oral or intravenous corticosteroids may be considered in cases of severe posterior uveitis such as vitritis and macular edema. However, long-term steroid use, particularly when it involves more than three drops daily, can lead to complications such as ocular hypertension, glaucoma, and cataracts. The high morbidity rate associated with corticosteroid therapy mandates the use of steroid-sparing immunosuppressive treatment at an earlier stage.[31]

Systemic treatment for uveitis in juvenile idiopathic arthritis

It is worth mentioning that even if arthritis itself might be severe and cause joint damage and long-term disability, uveitis often drives therapy choices. Systemic treatment should be started if ocular disease is persistent, lasting for more than 3 months, or if clinical inactivity could not be achieved with 3 drops or less of topical dexamethasone 0.1% or prednisolone acetate 1%, or if poor prognostic factors are present (ocular complications, male sex, and uveitis preceding arthritis).[56]

MTX is usually the first DMARD and is generally well tolerated and safe for long-term use as a steroid-sparing agent.[57] A meta-analysis of 9 studies described 135 children with uveitis associated with rheumatological diseases, of whom 121 JIA-U were treated with MTX (15 mg/m^2 the most commonly used dose).[57] The study showed that 95 children out of 135 included responded to the treatment according to the definition of improvement of the SUN working group criteria; a subanalysis targeted only on JIA patients estimated a 0.74 of MTX responders (95% CI 0.67–0.82).[57]

A retrospective study by Sobrin *et al*. suggests that mycophenolate mofetil (MMF) is effective in controlling inflammation after MTX failure or intolerance in slightly more than half the patients with ocular inflammatory disease. In this study, 47 patients (55%) achieved remission. However, 11 of these received additional immunosuppressive therapy. MMF also helped reduce the relapse rate (from 2.7 to 1.2 relapses/year). However, MMF has no role in treating arthritis.[58]

An accrual of evidence[59] is available to recommend standard dose 2 weekly ADA as a second line agent if MTX is not effective and/or not tolerated. A 2022 Cochrane review[60] encompassing three studies with a total of 134 randomized

participants investigated the effects of ADA and etanercept. Two studies focused on ADA (ADJUVITE and SYCAMORE), while one study examined etanercept (ETN). The ADJUVITE trial[61] involved 32 participants with JIA-U or idiopathic uveitis unresponsive to MTX therapy, randomized to receive either ADA or a placebo for 2 months, followed by an open-label phase of ADA for 6 months. The SYCAMORE[62] study reported on 115 eyes of 90 participants with JIA-U from the UK, with 30 participants randomized to the placebo group and 60 to the ADA group, continuing treatment until failure or for up to 18 months. Another study conducted in the USA enrolled 12 children (mean and median age of 11 years, ranging from 6 to 15 years old) with active uveitis with JIA and treated with ETN.[63] A pooled analysis of the three studies suggests that TNF inhibitors may increase the probability of treatment success (RR 2.60; 95% CI 1.30–5.20; 3 studies; 124 participants). Most of the evidence available was on ADA compared to placebo (RR 3.11; 95% CI 1.40–6.90; 2 studies; 112 participants), while the evidence on etanercept compared to placebo was very limited (RR 1.07; 95% CI 0.27–4.23; 1 study; 12 participants).

These results are corroborated by a comprehensive meta-analysis of 34 observational studies that included a total of 487 children: 226 were treated with ADA, 213 with INF, and 48 with etanercept (ETA). The response rates were 86% (95% CI: 76%, 95%) for ADA, 68% (95% CI: 50%, 85%) for INF, and 36% (95% CI: 9%, 67%) for ETA. The pooled analysis demonstrated significant differences among the treatments, with both ADA and INF showing superior efficacy compared to ETA ($\chi^2 = 26.8$, $P < 0.0001$ and $\chi^2 = 7.41$, $P < 0.006$, respectively). In addition, ADA was found to be significantly more effective than INF ($\chi^2 = 13.4$, $P < 0.0002$).[59]

Loss of efficacy may suggest the formation of antidrug antibodies,[64] but, if antibody positivity is not confirmed by laboratory tests, dose increasing[64] might be considered in case of loss of efficacy. In a retrospective case series on 42 children with CAU, 27/42 (64.3%) were treated with ADA. Escalation to weekly dosing of ADA was necessary for 11/27 children (40.7%). After 3 and 6 months, 7/11 children (63.6%) met the composite endpoint of inflammation control improvement based on several parameters including a two-level reduction in inflammation (or normalization to 0) of AC cells or aqueous flare or a 50% reduction in topical corticosteroid treatment.[65] If this strategy is not successful, another TNFi (excluding etanercept) or TOC should be the next therapeutic line. The preferred anti-TNF agent should be INF rather than golimumab or certolizumab[59] after ADA.

This is supported also by a single-center, retrospective study involving 27 pediatric patients with refractory (had previously failed treatment with ADA ± MTX) noninfectious uveitis, of whom 17 had JIA. Long-term administration of IFX over 9 months resulted in the control of uveitis in 89% of the patients and the control of arthritis in 76% (13 out of 17). In addition, there was a statistically significant reduction in the use of topical corticosteroids (percentage of patients on <2 drops of prednisolone acetate 1%/eye/day increased from 63% to 89% and 59% could discontinue steroid at the last FU visit) and glaucoma medications ($P = 0.0013$ OD and $P = 0.0278$ OS).[66]

Golimumab may be considered an option especially in those patients who develop a secondary failure to ADA. Two retrospective case series showed good outcomes in 4/7 and 5/10 of anti-TNF refractory CAU, respectively.[67,68]

Looking beyond TNF inhibitors, TOC is among the primary choices for managing refractory JIA-U. Several retrospective studies support the role of TOC in the treatment of CAU in children. Calvo-Río *et al*. reported a case series of 25 cases of refractory JIA-U treated with 8 mg/kg IV TOC every 4 weeks, finding a clinical response in 19 out of 25 (76%) patients. After a median FU of 12 months, visual improvement persisted, and complete remission of uveitis was observed in these 19 patients. A significant reduction in prednisone dosage was also achieved.[69] In another case series of 15 patients with refractory JIA-U, Tappeiner *et al*. achieved drug-induced remission in 10 patients after a mean of 5.7 months of 8 mg/kg IV TOC every 4 weeks. Uveitis recurred in three patients during FU, but remission persisted in the remaining seven patients (47%).[70] Marino *et al*. reported on 13 JIA patients treated with subcutaneous TOC (SC-TOC) for arthritis or uveitis. SC-TOC therapy was associated with a decrease in the rate of uveitis flares per year per patient from 1.6 ± 2.0 to 0.4 ± 0.7. Nine out of 13 patients (69%) required SC-TOC solely for active uveitis at baseline, and of these, 5 (56%) achieved complete treatment response. No uveitis relapses were observed in the 4 patients (31%) who required SC-TOC for active arthritis during FU (30.48 ± 21.6 months).[71]

Conflicting evidence on SC-TOC is provided by the phase 2 APTITUDE trial involving 21 patients with JIA-U refractory to MTX and at least one TNF inhibitor. The primary outcome was treatment response defined as a two-step decrease, or decrease to zero, from baseline in the level of inflammation (anterior chamber cells) at week 12. Among the 21 participants, only 34% (95% CI 25–57) responded to treatment ($P = 0.11$). Notably, all three patients with macular edema responded to TOC.[72]

Macular edema (CME) is a sight-threatening complication of JIA-U and indicates severe disease. While CME responds to corticosteroids, very high doses (topically, intravitreally, periorbitally, or systemically) are often required for control. Some evidence on adult patients suggests that IL-6 inhibitors may provide superior control of CME compared to TNF inhibitors.

A retrospective case series of patients with CAU refractory to steroids, at least one csDMARD, and in most cases, a biologic therapy reported 25 adult patients (9 with JIA) treated with TOC either as monotherapy ($n = 11$) or combined with conventional immunosuppressive drugs. Remission was achieved in 14 patients and therapy allowed steroid dose reduction.[73]

In another case series, seven patients with refractory CAU complicated by long-standing ME secondary to different conditions (3 JIA-U) showed progressive foveal thickness reduction during treatment with TOC and improvement in visual acuity. TOC therapy was withdrawn in two patients due to sustained remission at month 12. However, CME relapsed in both patients 3 months after TOC withdrawal, and reinitiation of TOC therapy led to good uveitis control and ME resolution.[74]

Leclercq *et al*. in a retrospective study comparing TNF inhibitors and TOC reported an overall response rate at 6 months of 46.2% (21.8% complete response) with anti-TNF-α agents and 58.5% (35.8% complete response) with TOC. In multivariate analysis, treatment with TOC (odds ratio, 2.10; 95% CI, 1.06–4.06; $P = 0.03$) was independently associated with complete response of uveitic ME compared to anti-TNF-α agents.[75]

Limited experience is available for abatacept and rituximab. Rituximab is a chimeric monoclonal antibody targeting CD20, a cell membrane molecule specifically expressed on B cells. This antibody interferes with the calcium ion regulatory function of CD20 leading to B-cell elimination. The precise role of B cells in uveitis remains unclear, which accounts for the infrequent use of rituximab in treating this condition. A case series by Miserocchi *et al*. reports eight patients treated with RTX with good response on uveitis (however, two patients had uncontrolled arthritis leading to therapy change).[76]

Evidence regarding abatacept use in JIA-U is restricted to few case reports and a case series reporting 21 patients with refractory CAU with 11 patients responding to ABA, of whom 8 subsequently relapsed.[77]

JAKi represents a promising class of drugs for the treatment of uveitis, however, evidence is so far limited to few case series. Currently, a multicenter randomized controlled trial comparing baricitinib to placebo for the management of ANA-positive CAU (JAHW trial NCT04088409) is ongoing; Miserocchi *et al*. described three patients treated with baricitinib and 1 with tofacitinib with positive outcome. Bauermann *et al*. reported a patient with uveitis complicated by macular edema successfully treated with tofacitinib.[78,79]

Conclusion

In recent years, several studies have explored risk factors, prognostic indicators, and potential therapies in patients with JIA-U. To date, despite advancements in the therapeutic era with more potent and advanced biological treatments, JIA and JIA-U remain significant therapeutic challenges for clinicians. Despite a variety of therapeutic options, optimal management for each patient often requires multiple attempts and close monitoring for secondary treatment failures. Enhanced understanding of JIA-U pathogenesis and its relationship with JIA will likely support the development of targeted medications in the future.

Currently, the management of JIA and JIA-U necessitates a collaborative approach between pediatric rheumatologists and ophthalmologists. The synergy between these specialists is crucial to ensure timely assessments, regular screening eye examinations, and necessary adjustments or escalations in therapy. This collaboration is essential to achieve the best possible outcomes for patients, emphasizing the importance of integrated care in managing these complex conditions.

In conclusion, JIA-U remains probably the most challenging and aggressive type of uveitis not only in the pediatric population but also among overall uveitis entities due to the early age of onset, the long-life chronicity of the disease, and the lack of therapeutic response in a fair amount of children, even despite new therapeutic agents available.

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Conflicts of interest

There are no conflicts of interest.

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