Turkish Archives of Pediatrics

REVIEW
DOI: 10.5152/TurkArchPediatr.2023.23086

An Overview of Pediatric Uveitis

İlknur Tuğal-Tutkun[1,2]

[1]Eye Protection Foundation Bayrampaşa Eye Hospital, İstanbul, Turkey
[2]Department of Ophthalmology, İstanbul University, İstanbul Faculty of Medicine, İstanbul, Turkey

ABSTRACT

Uveitis in childhood poses a distinct challenge, mainly because of the insidious onset and chronic course of intraocular inflammation in most cases, which may result in permanent visual loss due to delayed diagnosis and treatment. Although anterior uveitis, frequently associated with juvenile idiopathic arthritis, is the most common form of ocular involvement, idiopathic intermediate uveitis (pars planitis) is also a common uveitic entity in childhood. Posterior or panuveitis of a variety of noninfectious or infectious etiologies may be seen as well. Pediatric uveitis needs to be closely monitored since serious ocular complications such as intraocular pressure elevation, cataract, and macular edema may rapidly develop due to inadequately controlled inflammation and/or the use of corticosteroids. Methotrexate is generally the first-line corticosteroid-sparing agent, and adalimumab is the first-line biologic in refractory cases of noninfectious uveitis. A multidisciplinary approach is essential to monitor systemic disease associations, treatment response, and adverse events in children with uveitis.

Keywords: Pediatric uveitis, intraocular inflammation, iridocyclitis, methotrexate, adalimumab

INTRODUCTION

Uveitis is an umbrella term that defines inflammation of the intraocular structures, including the uveal tissues, iris, ciliary body, and choroid, as well as the nonuveal structures, retina, and vitreous. Although uveitis is rare in children, comprising 5%–10% of all uveitis cases,[1,2] there are uveitic entities that are exclusively or more commonly seen in children, rendering childhood uveitis a special group in uveitis practice. There are also distinct challenges in diagnosing and treating childhood uveitis, such as difficulties in the ocular examination of young children, the mostly asymptomatic nature of uveitis causing a delayed diagnosis, and the potential adverse effects of therapeutic agents on the growing child. Furthermore, ocular complications such as band keratopathy, cataract, and glaucoma are more common in children than in adults with uveitis, and young children are also prone to the risk of amblyopia.[3–5]

CLASSIFICATION OF UVEITIS

The Standardization of Uveitis Nomenclature (SUN) criteria are used for the classification of uveitis based on the anatomical location of intraocular inflammation as well as the onset, duration, and course of uveitis.[6] Anterior uveitis defines inflammation of the iris and ciliary body; the primary site of inflammation is the eye's anterior chamber. In intermediate uveitis, the vitreous is the primary site of inflammation which mainly involves the pars plana region of the ciliary body and the peripheral retina. Posterior uveitis defines retinal or choroidal inflammation as focal, multifocal, or diffuse. In panuveitis, all intraocular structures are affected. Clinical grading of inflammatory infiltration in the aqueous humor and vitreous allows for determining the severity of uveitis and monitoring response to treatment.[6]

Corresponding author:
İlknur Tuğal-Tutkun
✉ itutkun@yahoo.com
Received: April 20, 2023
Accepted: May 5, 2023
Publication Date: June 23, 2023

Cite this article as: Tuğal-Tutkun İ. An overview of pediatric uveitis. *Turk Arch Pediatr.* 2023;58(4):363-370.

The International Uveitis Study Group has published a clinical categorization of uveitis based on etiological criteria, including infectious uveitis, noninfectious uveitis with or without systemic disease association, and masquerade conditions (mimickers of uveitis) which can be neoplastic or nonneoplastic.[7]

EPIDEMIOLOGY AND ETIOLOGY OF PEDIATRIC UVEITIS

The incidence of childhood uveitis is around 4 per 100 000, and its prevalence is 28 per 100 000.[1] The etiological diagnosis of pediatric uveitis varies according to the geographic, ethnic, and genetic factors as well as the referral patterns of the population studied. While juvenile idiopathic arthritis (JIA) is the leading identifiable association of uveitis in most series reported from referral centers, the frequency of JIA-associated uveitis shows a wide range. It has been reported in 61% of children with uveitis in Finland,[8] 48% in Ireland,[9] 35% in the United States,[10] 25% in Israel,[11] 20% in Italy,[12] 12% in Turkey,[3] 9% in Iran,[13] and 6% in Egypt and Tunisia.[14,15] In the Far East, JIA uveitis comprised 15% of childhood uveitis in Korea[16] and 8% in China,[17] but was reported in only 1.7% in Thailand[18] and none of the patients in Japan.[19] Idiopathic uveitis without any identifiable cause or systemic disease association is more common in children than in adults,[1] comprising more than 50% of cases in series reported from Israel, Korea, China, and Japan.[11,16,17,19] While the frequency of infectious uveitis was 3.5% in a US series,[10] it was 58% in a series reported from Columbia, where toxoplasmosis was the leading cause (76.8%), followed by toxocariasis (17.7%).[20] Toxoplasmosis is the most common infectious etiology in several other countries as well, but the overall rates are much lower, reported in 7-15% of all childhood uveitis cases.[3,12-15,18] On the other hand, tuberculosis is the leading cause of infectious pediatric uveitis in India, accounting for more than 50% of infectious cases.[21]

Anterior uveitis is the most common anatomic form of uveitis in children, mostly associated with JIA, especially in North America and Northern Europe,[8-10] but also can be idiopathic.[19,22] Intermediate uveitis is almost always idiopathic in children and is defined as "pars planitis."[6,23,24] The most common systemic associations of panuveitis include Behçet disease and Vogt-Koyanagi-Harada (VKH) disease in countries with a high prevalence of these entities in the adult population as well.[3,18,19]

In a multicenter uveitis registry study in Turkey, pars planitis was the most common diagnosis in children (22%), followed by JIA (12%) and Behçet disease (9%).[3] An infectious uveitis was diagnosed in 15.6% of children, toxoplasmosis being the most common etiology (8%) followed by herpetic anterior uveitis (3%). Apart from 9% of cases where a diagnosis could not be established, 17% were diagnosed as idiopathic uveitis, and 67% of them had the anterior form.[3] Overall, the most common anatomic form was anterior uveitis (39%), followed by intermediate uveitis (29%).[3]

CLINICAL EVALUATION, MONITORING, AND IMAGING OF UVEITIS IN CHILDREN

Slit-lamp examination is essential and can be performed even in a very young child. Band keratopathy, corneal endothelial deposits of inflammatory cells defined as keratic precipitates (KPs), cells and flare (protein) in the anterior chamber, pupillary adhesions to the anterior lens capsule (posterior synechiae), lens opacities, and vitreous cells and opacities can best be detected at the slit-lamp examination. Indirect fundus examination is also preferably performed at the slit-lamp after pharmacologic dilation of the pupils. Intraocular pressure (IOP) measurements should be obtained at each visit with a method that is most acceptable to the child. The SUN grade of intraocular inflammation should be recorded at each visit. Slit-lamp photographs should be periodically taken to document and follow complications such as band keratopathy and posterior synechiae (Figure 1). Fundus photographs should be taken to document retinochoroidal lesions.

Laser flare photometry (LFP) is a noninvasive, objective, and quantitative method to measure flare in the anterior chamber (protein content in the aqueous humor).[25] Children who can cooperate at slit-lamp examination can also get their flare measured by LFP. High LFP flare values have been found to be associated with a higher risk of ocular complications, and a 50% or more reduction of flare after treatment was shown to be associated with a lower risk of complications at long-term follow-up.[26-28]

Optical coherence tomography (OCT) is also a noninvasive tool that is routinely used to detect and monitor macular edema. It allows both qualitative and quantitative evaluation of macular edema, which is the most frequent cause of visual loss in patients with uveitis.[29] Maculopathy could be detected by OCT imaging in up to 84% of eyes with JIA uveitis.[30]

Anterior segment OCT is a relatively new method to quantify cells in the anterior chamber and needs to be standardized for routine use.[31]

Fundus fluorescein angiography (FFA) shows leakage from inflamed retinal vasculature, retinal nonperfusion due to occlusive vasculitis, and staining and leakage characteristics of retinochoroidal lesions.[32] It is routinely performed by intravenous injection of fluorescein dye. In young children, oral administration of fluorescein also allows the detection of significant leakage and edema in the fundus[33]; however, subtle leakage may be missed.[34] Subclinical–occult–retinal vasculitis can only be revealed by FFA.[34] Wide or ultrawide field FFA is used to better visualize the peripheral retina in uveitis patients.[32-34]

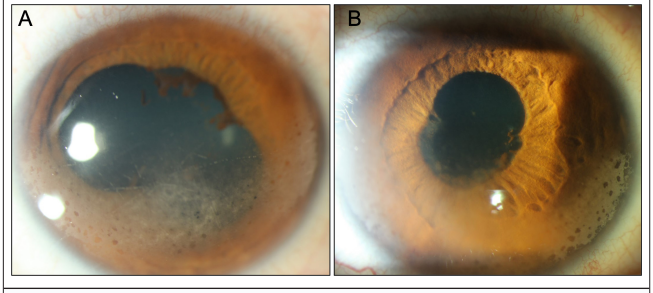

Figure 1. Slit-lamp photographs show band keratopathy and posterior synechiae (adhesions of the pupil to the anterior surface of the lens) in the right (A) and the left eye (B) of a girl with chronic anterior uveitis associated with rheumatoid-factor-negative polyarticular juvenile idiopathic arthritis.

Indocyanine green angiography is the imaging method of choice to visualize choroidal inflammation. Intravenous injection of the indocyanine dye is required. Indocyanine green angiography is essential to detect subclinical choroidal inflammation and monitor response to therapy.[35]

Optical coherence tomography-angiography is a relatively new imaging system utilized for the noninvasive visualization of the retinal and choroidal circulation, especially at the capillary level.[36] As it does not show leakage, the most important marker of vascular inflammation, its use is limited in pediatric uveitis.

ANTERIOR UVEITIS

Chronic anterior uveitis is the most common form of uveitis in children, and it is mostly asymptomatic until the development of severe ocular complications causing profound loss of vision. These children may also first present with a secondary squint. The absence of red eyes, tearing or photophobia, preserved visual acuity in the early stages of the disease, as well as preverbal age of the child are the main causes of delayed diagnosis. In fact, children with idiopathic chronic anterior uveitis are more likely to present with complications due to diagnostic delay than those with JIA-associated chronic anterior uveitis, as the latter group is routinely screened for eye involvement.[22] The same is true for children with the onset of uveitis prior to the onset of JIA.

Children with acute anterior uveitis typically present with red eyes, photophobia, and tearing. They may be initially misdiagnosed as conjunctivitis unless a careful slit-lamp examination is performed. There would be no response to initially prescribed antibiotic drops, and symptoms would worsen without proper treatment with topical steroids and cycloplegic agents.

Chronic or acute anterior uveitis may be granulomatous or nongranulomatous. When there are large corneal endothelial deposits of inflammatory cells (mutton-fat KPs) and/or iris nodules, the clinical picture is defined as granulomatous. In nongranulomatous anterior uveitis, corneal endothelial dusting or fine KPs are seen. In all forms of anterior uveitis in children, posterior synechiae may develop rapidly; therefore, proper treatment should be promptly started.

While nongranulomatous chronic anterior uveitis is typically seen in children with JIA, acute nongranulomatous anterior uveitis is exclusively seen in enthesitis-related arthritis (ERA), mostly associated with the HLA-B27 antigen. Psoriatic arthritis is associated with chronic anterior uveitis in young children but typically with acute anterior uveitis in older children and adolescents.[37] In a Turkish multicenter retrospective cohort of 500 JIA patients, the most common JIA category was oligoarticular JIA (39%), followed by ERA (23%).[38] Uveitis was diagnosed in 6.8% of the whole cohort, being most common in oligoarticular JIA (12.9%), followed by ERA (5.2%) and polyarticular RF-negative JIA (3.8%). Uveitis developed within 2 years after the diagnosis of JIA in 50%. Patients with extended oligoarticular JIA and ANA-positive oligoarticular JIA had a higher risk of uveitis than those with polyarticular JIA and ANA-negative oligoarticular JIA, respectively.[38] In a retrospective American cohort of 287 JIA patients, uveitis was reported in 18%, who were diagnosed with JIA at a mean age of 2.8 years and with uveitis at 4.8 years.[39] Uveitis was diagnosed prior to JIA in 24% of them. Patients with uveitis were younger at JIA diagnosis and likely to have ANA-positive persistent oligoarticular JIA.[39] In both cohorts, the majority of children had bilateral anterior uveitis. There was at least one ocular complication in 50% of children with uveitis in the American cohort.[39] Surgical treatment for uveitis-related complications was required in 15% of cases in the Turkish cohort.[38]

Kawasaki disease may be the cause of bilateral nongranulomatous anterior uveitis in young children. Tubulointerstitial nephritis and uveitis (TINU) syndrome is usually seen in older children and adolescents, with a median age of 15 years.[40] While bilateral symptomatic acute-onset nongranulomatous anterior uveitis is the typical form in TINU, granulomatous anterior uveitis may be seen as well, and involvement of the posterior segment of the eye has been reported in up to 65% of the cases.[41] A chronic granulomatous anterior uveitis should prompt a differential diagnosis including early-onset sarcoidosis or Blau syndrome and tuberculosis. In a child presenting with unilateral acute granulomatous anterior uveitis with raised IOP, viral anterior uveitis should first be considered.

INTERMEDIATE UVEITIS

Children with idiopathic intermediate uveitis (pars planitis) usually present with floaters due to vitreous cells and opacities. They may also present with a significant reduction in visual acuity due to macular edema or vitreous opacification or even bleeding into the vitreous from neovascularizations as a result of long-standing intraocular inflammation. However, young children with pars planitis are often asymptomatic until late in the disease course because of the absence of red eyes, ocular pain, photophobia, or tearing.

Intermediate uveitis is bilateral in the majority of cases, but there may be asymmetrical involvement in some patients, with one eye showing more severe inflammation with a dense vitreous haze, snowball opacities in the vitreous, snowbank type of inflammatory infiltrate in the inferior peripheral retina, and optic disc and macular edema, while the other eye having only vitreous cells without haze. When there is accompanying severe anterior uveitis, as is the case, especially in childhood pars planitis, it is defined as intermediate and anterior uveitis rather than panuveitis.[6] Figure 2 shows multimodal ocular imaging in a young child with intermediate and anterior uveitis. Visual prognosis is relatively favorable despite the high rate of ocular complications.[23,24]

Intermediate uveitis in childhood is occasionally associated with a systemic disease such as sarcoidosis, tuberculosis, multiple sclerosis, Lyme disease, TINU, or inflammatory bowel disease; therefore, patients should be investigated for any associated condition.[42]

POSTERIOR UVEITIS

Focal, multifocal, or diffuse chorioretinal scars and pigmentary changes are the most common manifestations of congenital infections caused by toxoplasma, cytomegalovirus (CMV), herpes simplex virus (HSV), rubella virus, lymphocytic choriomeningitis virus, and zika virus.[43,44] With perinatally

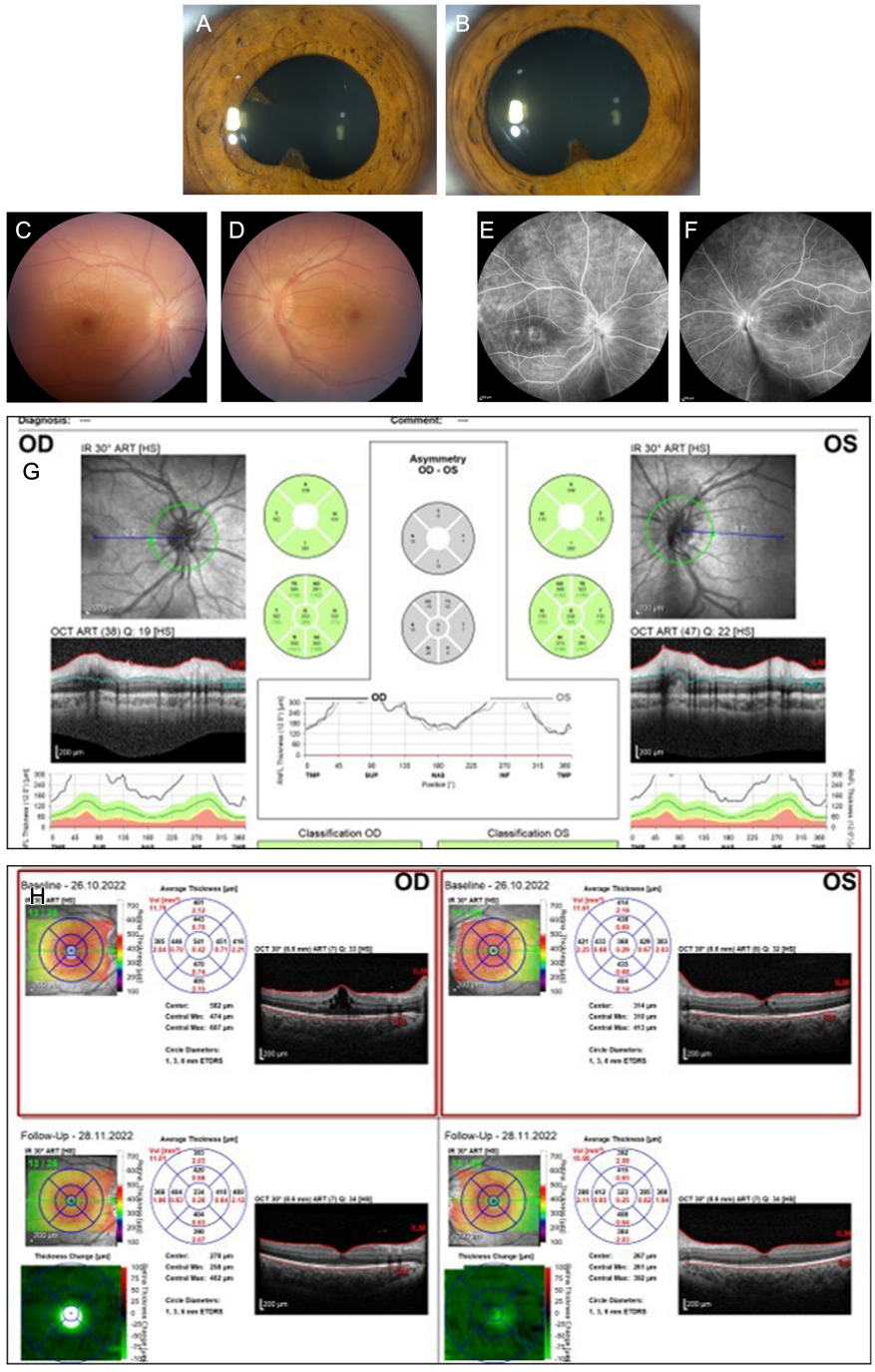

Figure 2. Multimodal ocular imaging in a 7-year-old boy with pars planitis: Slit-lamp photographs show posterior synechiae in the right (A) and the left eye (B); color fundus photographs show mild vitreous haze and optic disc edema in both eyes (C, D); fundus fluorescein angiography shows optic disc hyperfluorescence, cystoid macular edema, and diffuse capillary leakage, more severe in the right (E) than in the left eye (F). Optical coherence tomography imaging and automatic quantification show marked thickening of the retinal nerve fiber layer in both eyes (G); follow-up imaging of the macula shows cystoid macular edema more severe in the right eye at presentation and its resolution after treatment (H).

acquired infection, infants may be seen with active severe retinitis as well.

Toxoplasmic retinochoroiditis is the most common infectious posterior uveitis due to the reactivation of congenital infection or associated with acquired infection later in childhood.[45] Bilateral macular scars are typically associated with congenital toxoplasmosis. Reactivations involving the posterior pole or the optic disc may cause significant loss of vision. Diagnosis is based on clinical findings and the detection of anti-toxoplasma IgG antibodies in the serum. Treatment is with anti-parasitic agents coupled with corticosteroids. There is a lifetime risk of reactivation of toxoplasmic retinochoroiditis due to the absence of effective treatment for dormant toxoplasma cysts in the retina.[46] Therefore, children with toxoplasmic retinochoroidal scars need to be followed.

Ocular toxocariasis is more commonly seen in children than in adults and may present in the form of unilateral posterior pole or peripheral granuloma or endophthalmitis. Posterior pole granuloma is the most common presentation in young children. Diagnosis is based on clinical suspicion and serological tests.

While viral necrotizing retinitis caused by HSV or varicella-zoster virus is rare in children, CMV retinitis may develop in children with congenital immunodeficiencies or acquired immunocompromised states such as hematological malignancies or post-chemotherapy.[47] Definitive diagnosis of viral retinitis is based on the detection of viral antigens in intraocular fluids. Subacute sclerosing panencephalitis may first present with optic neuritis or macular necrotizing retinitis. Its diagnosis is based on the finding of elevated measles IgG antibodies in the cerebrospinal fluid.[48] Children may also rarely present with postinfectious retinal vasculitis, usually accompanied by anterior uveitis following chickenpox or influenza.

Tuberculosis, brucellosis, and syphilis must be ruled out in all children and adolescents who present with retinochoroidal inflammatory lesions with or without accompanying anterior uveitis. Sarcoidosis may be the systemic association of posterior uveitis in older children, whereas, in younger children presenting with skin rash, arthritis, and bilateral multifocal choroiditis, Blau syndrome should be considered. In children presenting with bilateral exudative retinal detachment secondary to diffuse choroiditis, acute VKH disease should first be considered in the diagnosis.

PANUVEITIS

Since both anterior and posterior segments of the eye can be severely inflamed in panuveitis, the risk of visual loss is higher than in other forms of uveitis.

Panuveitis and retinal vasculitis associated with Behçet disease is a potentially blinding disorder in children as in adults and needs to be aggressively treated.[49] Onset of uveitis is in late childhood, it is more common in males, and there is a high rate of family history in pediatric Behçet patients.[49,50] Children may first present with uveitis and fulfill the diagnostic/classification criteria for Behçet disease later in the disease course.[51] Clinical ocular features are similar to the adult group, with bilateral involvement, a relapsing and remitting course of nongranulomatous panuveitis, occlusive and leaky retinal vasculitis, and retinal infiltrations in the majority of patients.

In children, VKH disease is usually diagnosed late in the disease course when it presents with bilateral chronic recurrent granulomatous panuveitis. Diagnosis of VKH disease at this stage is based on clinical features, including bilateral granulomatous anterior uveitis, choroidal atrophy, and diffuse pigmentary changes in the fundus, as well as integumentary signs of the disease, including vitiligo, poliosis, and alopecia. These children also require long-term immunomodulatory therapy to prevent blinding complications of chronic intraocular inflammation.[52,53]

In an international case series of 50 patients with Blau syndrome-associated uveitis, none of the patients had isolated eye disease, the mean age at onset of ocular involvement was 60 months, and 51% of the eyes had panuveitis, and the risk of developing panuveitis increased with longer disease duration.[54] The most common fundus finding was multifocal chorioretinal lesions (39%), followed by optic disc changes (29%). Anterior segment complications such as band keratopathy, posterior synechiae, and cataract were also frequently seen in this patient group.[54]

TREATMENT OF NONINFECTIOUS UVEITIS IN CHILDREN

Corticosteroids are generally used as the first line for treating active intraocular inflammation. Topical, periocular, intravitreal, or systemic administration of corticosteroids may be chosen, singly or in combination, according to the anatomic location, laterality, and severity of intraocular inflammation. It is of utmost importance to keep in mind that children are especially prone to the complications of corticosteroid therapy, including ocular complications, cataract, and elevated IOP leading to steroid-induced glaucoma, as well as systemic complications, especially weight gain, growth retardation, and adrenal suppression in the long-term. In children, use of topical corticosteroids more than 2 drops daily for an extended period is associated with the risk of cataract development.[55] In a randomized controlled trial, IOP elevation was recorded in 71% of children who received dexamethasone 0.1% drops 4 times daily and 59% of those on twice daily for 4 weeks.[56] Intraocular pressure rise was earlier and higher in children younger than 6 years of age. Periocular and intravitreal depot corticosteroid injections and intravitreal corticosteroid implants are administered only as a last resort, mainly for the treatment of persistent macular edema, because of the higher risk of glaucoma and cataract development and also because of the need for general anesthesia for such procedures especially in young children.

In children who present with bilateral severe intraocular inflammation, especially in those who present with intermediate, posterior, or panuveitis, high-dose short-term systemic corticosteroids can be safely used in order to rapidly suppress the intraocular inflammation and regain potential visual acuity. It can be started with intravenous methylprednisolone up to 30 mg/kg per infusion and continued with oral prednisolone 1-2 mg/kg with subsequent tapering. Long-term oral corticosteroid therapy even at a low dose should be avoided in children. Therefore, early administration of corticosteroid-sparing disease-modifying antirheumatic drugs (DMARDs) is required in children with chronic uveitis.

Among conventional DMARDs, methotrexate, an antimetabolite, is usually the first drug of choice because of its long track record for safety and efficacy in children with uveitis. Subcutaneous weekly injections of methotrexate are better tolerated and provide higher bioavailability than a weekly oral regimen.[1] Its slow onset of action, taking 3-4 months for its full effect, and the development of aversion to the drug in the long term are the major drawbacks of methotrexate therapy. A folic acid supplement is given to prevent side effects, including bone marrow, hepatic, and gastrointestinal toxicity. Longer than 3 years of methotrexate therapy and longer than 2 years of inactivity of uveitis before methotrexate discontinuation are associated with higher chances of drug-free remission in children with JIA-associated uveitis.[57] In children who do not

tolerate methotrexate, the other antimetabolites, azathioprine or mycophenolate, may be tried, with moderate efficacy.

In 2 double-blind, randomized placebo-controlled trials, the efficacy of subcutaneous adalimumab has been proven in children with JIA-associated or idiopathic chronic anterior uveitis who had active inflammation despite treatment with methotrexate.[58,59] In the SYCAMORE Trial, the addition of adalimumab to methotrexate significantly delayed the time to treatment failure, and the rate of treatment failure was lower in the adalimumab group (27%) than in the placebo group (60%).[58] In the ADJUVITE trial, at least a 30% reduction of LFP flare was achieved in a significantly higher percentage of patients in the adalimumab group than in the placebo group (64% versus 20% in the per-protocol population).[59] Based on these trials, adalimumab has been approved and became the first-line biologic for the treatment of refractory chronic anterior uveitis in children. The standard dosing regimen is 20 mg in children weighing <30 kg or 40 mg in children weighing ≥30 kg administered every other week. In subsequent reports, weekly dosing was effective and safe in children who did not respond to the standard dose.[60,61] Adalimumab is effectively used in the treatment of other noninfectious, non-JIA, anterior uveitis as well as intermediate, posterior, or panuveitis in children with or without systemic disease association.[62,63] Peripheral retinal vascular leakage on FFA could be alleviated by adalimumab treatment in children with chronic anterior uveitis and retinal vascular leakage.[64] In children with intermediate uveitis, multiple sclerosis needs to be ruled out first, and patients should also be followed by neurologists during adalimumab therapy. A recent meta-analysis showed that adalimumab has a significant corticosteroid-sparing effect and a good long-term safety profile.[65]

In patients who fail adalimumab therapy, switching to other anti-TNF agents may be considered, such as infliximab, golimumab, or certolizumab. Infliximab infusions have also been used as the initial line of treatment for immediate control of severe intraocular inflammation in children.[66] High-dose infusions (10 mg/kg or more every 4 weeks) may be needed in children with severe uveitis.[67] While switching to golimumab was reported to be beneficial in case of loss of response to adalimumab in JIA-associated uveitis, the switch was not successful in primary unresponsiveness to adalimumab.[68] Alternative biologic agents such as tocilizumab, abatacept, or rituximab may be tried when anti-TNF agents are not successful.[69,70] Although the primary endpoint was not met in a multicenter, single-arm, phase 2 trial of tocilizumab in patients with anti-TNF refractory JIA-associated uveitis (APTITUDE Trial), 7 of 21 enrolled patients responded to treatment, suggesting that tocilizumab may still be an alternative biologic in case of anti-TNF failure.[71]

In children who achieve uveitis quiescence after treatment with biological agents, the optimum duration of therapy is not known. A high relapse rate has been reported after discontinuation of anti-TNF treatment, irrespective of the duration of treatment.[72,73] The international multicenter placebo-controlled Adalimumab in Juvenile Idiopathic Arthritis-associated Uveitis Stopping Trial (ADJUST Trial) will compare the time to uveitis recurrence between patients who are maintained on adalimumab versus those given placebo after remission of JIA uveitis is achieved with adalimumab therapy of at least 12 months.[74]

There is an ongoing international, multicenter, open-label, adalimumab active-controlled phase-III trial (JUVE-BRIGHT) that will investigate the safety and efficacy of baricitinib, an oral selective Janus kinase (JAK)1 and 2 inhibitor, in patients with active JIA-associated or ANA-positive chronic uveitis who have an inadequate response or intolerance to methotrexate.[75]

While guidelines or consensus treatment plans have been published for idiopathic or JIA-associated chronic anterior uveitis,[76-78] there are currently no such consensus guidelines for the treatment of nonanterior forms of uveitis in children.

CONCLUSIONS

While an infectious etiology has to be ruled out in all children presenting with uveitis, the majority have chronic noninfectious uveitis, which is a major burden on the growing children and their families. Without prompt and adequate control of intraocular inflammation, there is a high risk of visual loss due to severe ocular complications, resulting in lifelong disability. Close monitoring of uveitis activity by an experienced ophthalmologist, using also multimodal ocular imaging techniques, will ensure timely interventions with more effective therapeutic modalities. A multidisiciplinary approach is essential for a thorough investigation of any underlying disease and for the long-term management of children with uveitis, even those initially diagnosed as idiopathic uveitis, because extraocular manifestations may develop later in the disease course, and most importantly, the well-being of the child, growth rate, adherence to treatment, drug dosing, toxicity, and adverse events need to be closely monitored.

Peer-review: Externally peer-reviewed.

Declaration of Interests: İlknur Tuğal-Tutkun has received consultancy and lecture fees from AbbVie, Turkey, and consultancy fees from Amgen, Turkey.

Funding: This study received no funding.

REFERENCES

1. Maleki A, Anesi SD, Look-Why S, Manhapra A, Foster CS. Pediatric uveitis: a comprehensive review. *Surv Ophthalmol*. 2022;67(2):510-529. [CrossRef]
2. Yalçındağ FN, Özdal PC, Özyazgan Y, Batıoğlu F, Tugal-Tutkun I, BUST Study Group. Demographic and clinical characteristics of uveitis in Turkey: the First National registry report. *Ocul Immunol Inflammm*. 2018;26(1):17-26. [CrossRef]
3. Yalçındağ FN, Özdal P, Özyazgan Y, Batıoğlu F, Tugal-Tutkun I, BUST Study Group. Pediatric uveitis in Turkey: the national registry Report II. *Ocul Immunol Inflammm*. 2022:1-7. [CrossRef]
4. Smith JA, Mackensen F, Sen HN, et al. Epidemiology and course of disease in childhood uveitis. *Ophthalmology*. 2009;116(8):1544-1551. [CrossRef]
5. Rosenberg KD, Feuer WJ, Davis JL. Ocular complications of pediatric uveitis. *Ophthalmology*. 2004;111(12):2299-2306. [CrossRef]
6. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) working group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005;140(3):509-516.
7. Deschenes J, Murray PI, Rao NA, Nussenblatt RB, International Uveitis Study Group. International Uveitis Study Group (IUSG):

clinical classification of uveitis. *Ocul Immunol Inflammm.* 2008;16(1):1-2. [CrossRef]
8. Siiskonen M, Hirn I, Pesälä R, Hautala T, Ohtonen P, Hautala N. Prevalence, incidence and epidemiology of childhood uveitis. *Acta Ophthalmol.* 2021;99(2):e160-e163. [CrossRef]
9. Curragh DS, O'Neill M, McAvoy CE, Rooney M, McLoone E. Pediatric uveitis in a well-defined population: improved outcomes with immunosuppressive therapy. *Ocul Immunol Inflammm.* 2018;26(6):978-985. [CrossRef]
10. Ferrara M, Eggenschwiler L, Stephenson A, et al. The challenge of pediatric uveitis: tertiary referral center experience in the United States. *Ocul Immunol Inflammm.* 2019;27(3):410-417. [CrossRef]
11. Habot-Wilner Z, Tiosano L, Sanchez JM, et al. Demographic and clinical features of pediatric uveitis in Israel. *Ocul Immunol Inflammm.* 2020;28(1):43-53. [CrossRef]
12. Paroli MP, Spinucci G, Liverani M, Monte R, Pezzi PP. Uveitis in childhood: an Italian clinical and epidemiological study. *Ocul Immunol Inflammm.* 2009;17(4):238-242. [CrossRef]
13. Rahimi M, Oustad M, Ashrafi A. Demographic and clinical features of pediatric uveitis at a Tertiary Referral Center in Iran. *Middle East Afr J Ophthalmol.* 2016;23(3):237-240. [CrossRef]
14. Abd El Latif E, Fayez Goubran W, El Gemai EEDM, et al. Pattern of childhood uveitis in Egypt. *Ocul Immunol Inflammm.* 2019;27(6):883-889. [CrossRef]
15. Khairallah M, Attia S, Zaouali S, et al. Pattern of childhood-onset uveitis in a referral center in Tunisia, North Africa. *Ocul Immunol Inflammm.* 2006;14(4):225-231. [CrossRef]
16. Shin Y, Kang JM, Lee J, Lee CS, Lee SC, Ahn JG. Epidemiology of pediatric uveitis and associated systemic diseases. *Pediatr Rheumatol Online J.* 2021;19(1):48. [CrossRef]
17. Sun N, Wang C, Linghu W, Li X, Zhang X. Demographic and clinical features of pediatric uveitis and scleritis at a tertiary referral center in China. *BMC Ophthalmol.* 2022;22(1):174. [CrossRef]
18. Seepongphun U, Sittivarakul W, Dangboon W, Chotipanvithayakul R. The pattern of uveitis in a pediatric population at a Tertiary Center in Thailand. *Ocul Immunol Inflammm.* 2023;31(1):56-64. [CrossRef]
19. Keino H, Watanabe T, Taki W, et al. Clinical features of uveitis in children and adolescents at a tertiary referral centre in Tokyo. *Br J Ophthalmol.* 2017;101(4):406-410. [CrossRef]
20. Lonngi M, Aguilar MC, Ríos HA, Aristizábal-Duque CH, Rodríguez FJ, de-la-Torre A. Pediatric uveitis: experience in Colombia. *Ocul Immunol Inflammm.* 2016;24(4):410-414. [CrossRef]
21. Gautam N, Singh R, Agarwal A, et al. Pattern of pediatric uveitis at a tertiary referral institute in North India. *Ocul Immunol Inflammm.* 2018;26(3):379-385. [CrossRef]
22. Kouwenberg CV, Wennink RAW, Shahabi M, Bozkir I, Ayuso VK, de Boer JH. Clinical course and outcome in pediatric idiopathic chronic anterior uveitis. *Am J Ophthalmol.* 2022;241:198-205. [CrossRef]
23. de Boer J, Berendschot TT, van der Does P, Rothova A. Long-term follow-up of intermediate uveitis in children. *Am J Ophthalmol.* 2006;141(4):616-621. [CrossRef]
24. AlBloushi AF, Solebo AL, Gokhale E, Hayouti H, Ajamil-Rodanes S, Petrushkin H. Long-term outcomes of pediatric idiopathic intermediate uveitis. *Am J Ophthalmol.* 2022;237:41-48. [CrossRef]
25. Tugal-Tutkun I, Herbort CP. Laser flare photometry: a noninvasive, objective, and quantitative method to measure intraocular inflammation. *Int Ophthalmol.* 2010;30(5):453-464. [CrossRef]
26. Orès R, Terrada C, Errera MH, et al. Laser flare photometry: a useful tool for monitoring patients with juvenile idiopathic arthritis-associated uveitis. *Ocul Immunol Inflammm.* 2022;30(1):118-128. [CrossRef]
27. Davis JL, Dacanay LM, Holland GN, Berrocal AM, Giese MJ, Feuer WJ. Laser flare photometry and complications of chronic uveitis in children. *Am J Ophthalmol.* 2003;135(6):763-771. [CrossRef]
28. Yalçındağ FN, Köse HC, Temel E. Comparative study of laser flare photometry versus slit-lamp cell measurement in pediatric chronic non-infectious anterior uveitis. *Eur J Ophthalmol.* 2023;33(1):382-390. [CrossRef]
29. de Boer J, Steijaert A, van den Bor R, Stellato R, Ossewaarde-van Norel J. Development of macular edema and impact on visual acuity in uveitis associated with juvenile idiopathic arthritis. *Ocul Immunol Inflammm.* 2015;23(1):67-73. [CrossRef]
30. Ducos de Lahitte G, Terrada C, Tran TH, et al. Maculopathy in uveitis of juvenile idiopathic arthritis: an optical coherence tomography study. *Br J Ophthalmol.* 2008;92(1):64-69. [CrossRef]
31. Etherton K, Rahi JS, Petrushkin H, et al. Quantitative and qualitative assessment of anterior segment optical coherence tomography capture of disease state in childhood anterior uveitis. *Br J Ophthalmol.* 2022. [CrossRef]
32. Hossain HA, Ye S, Ward L, O'Keefe GD. Characterization of fluorescein angiography features in pediatric patients with uveitis. *Ocul Immunol Inflammm.* 2022:1-5. [CrossRef]
33. Jiang Z, Sun L, Hou A, et al. Oral fluorescein angiography with ultra-wide-field scanning laser ophthalmoscopy in pediatric patients precis: oral fluorescein angiography in children. *J Clin Med.* 2022;11(18):5421. [CrossRef]
34. Abraham A, Saboo US, Ducca BL, Lawand AT, Ronconi C, Cao JH. The detection of occult retinal vasculitis on fluorescein angiography in pediatric uveitis. *Ophthalmol Retina.* 2020;4(2):198-203. [CrossRef]
35. Scifo L, Willermain F, Postelmans L, et al. Subclinical choroidal inflammation revealed by indocyanine green angiography in tubulointerstitial nephritis and uveitis syndrome. *Ocul Immunol Inflammm.* 2022;30(5):1190-1198. [CrossRef]
36. Qu Y, Zhao C, Pei M, Liang A, Gao F, Zhang M. Anterior segment inflammation in pediatric uveitis is associated with reduced retinal vascular density as quantified by optical coherence tomography angiography. *Ocul Immunol Inflammm.* 2022;30(2):392-396. [CrossRef]
37. Tugal-Tutkun I, Quartier P, Bodaghi B. Disease of the year: juvenile idiopathic arthritis-associated uveitis--classification and diagnostic approach. *Ocul Immunol Inflammm.* 2014;22(1):56-63. [CrossRef]
38. Sahin S, Acari C, Sonmez HE, et al. Frequency of juvenile idiopathic arthritis and associated uveitis in pediatric rheumatology clinics in Turkey: a retrospective study, Jupiter. *Pediatr Rheumatol Online J.* 2021;19(1):134. [CrossRef]
39. Angeles-Han ST, McCracken C, Yeh S, et al. Characteristics of a cohort of children with Juvenile Idiopathic Arthritis and JIA-associated uveitis. *Pediatr Rheumatol Online J.* 2015;13:19. [CrossRef]
40. Amaro D, Carreño E, Steeples LR, Oliveira-Ramos F, Marques-Neves C, Leal I. Tubulointerstitial nephritis and uveitis (TINU) syndrome: a review. *Br J Ophthalmol.* 2020;104(6):742-747. [CrossRef]
41. Koreishi AF, Zhou M, Goldstein DA. Tubulointerstitial nephritis and uveitis syndrome: characterization of clinical features. *Ocul Immunol Inflammm.* 2021;29(7-8):1312-1317. [CrossRef]
42. Heinz C, Schoonbrood S, Heiligenhaus A. Intermediate uveitis in children and young adults: differences in clinical course, associations and visual outcome. *Br J Ophthalmol.* 2014;98(8):1107-1111. [CrossRef]
43. Mets MB, Chhabra MS. Eye manifestations of intrauterine infections and their impact on childhood blindness. *Surv Ophthalmol.* 2008;53(2):95-111. [CrossRef]
44. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, et al. Ocular findings in infants with microcephaly associated with presumed zika virus congenital infection in Salvador, Brazil. *JAMA Ophthalmol.* 2016;134(5):529-535. [CrossRef]
45. Hettinga YM, de Groot-Mijnes JD, Rothova A, de Boer JH. Infectious involvement in a tertiary center pediatric uveitis cohort. *Br J Ophthalmol.* 2015;99(1):103-107. [CrossRef]

46. Kalogeropoulos D, Sakkas H, Mohammed B, et al. Ocular toxoplasmosis: a review of the current diagnostic and therapeutic approaches. *Int Ophthalmol.* 2022;42(1):295-321. [CrossRef]
47. Sadik MT, Aksu Ceylan N, Cebeci Z, Kir N, Oray M, Tugal-Tutkun I. Patterns of cytomegalovirus retinitis at a tertiary referral center in Turkey. *Int Ophthalmol.* 2021;41(9):2981-2992. [CrossRef]
48. Oray M, Tuncer S, Kir N, Karacorlu M, Tugal-Tutkun I. Optic neuritis and rapidly progressive necrotizing retinitis as the initial signs of subacute sclerosing panencephalitis: a case report with clinical and histopathologic findings. *Int Ophthalmol.* 2014;34(4):983-987. [CrossRef]
49. Tugal-Tutkun I, Urgancioglu M. Childhood-onset uveitis in Behçet disease:a descriptive study of 36 cases. *Am J Ophthalmol.* 2003;136(6):1114-1119. [CrossRef]
50. Demir F, Sönmez HE, Bağlan E, et al. Cluster analysis of paediatric Behçet's disease: data from the Pediatric Rheumatology Academy-Research Group. *Mod Rheumatol.* 2023;33(3):574-578. [CrossRef]
51. Koné-Paut I, Shahram F, Darce-Bello M, et al. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. *Ann Rheum Dis.* 2016;75(6):958-964. [CrossRef]
52. Kaza H, Tyagi M, Agarwal K, et al. Vogt Koyanagi Harada Disease In Paediatric Age Group: Clinical characteristics, remission, recurrences and complications in Asian Indian population. *Semin Ophthalmol.* 2022;37(2):187-192. [CrossRef]
53. AlBloushi AF, AlEnezi SH, Al Owaifeer AM, Al-Hadlaq OS, Gikandi PW, Abu El-Asrar AM. Long-term outcomes of uveitis associated with Vogt-Koyanagi-Harada disease in the pediatric age group. *Ocul Immunol Inflammm.* 2022;30(7-8):1669-1677. [CrossRef]
54. Sarens IL, Casteels I, Anton J, et al. Blau syndrome-associated uveitis: preliminary results from an international prospective interventional case series. *Am J Ophthalmol.* 2018;187:158-166. [CrossRef]
55. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. *Ophthalmology.* 2010;117(7):1436-1441. [CrossRef]
56. Lam DS, Fan DS, Ng JS, Yu CB, Wong CY, Cheung AY. Ocular hypertensive and anti-inflammatory responses to different dosages of topical dexamethasone in children: a randomized trial. *Clin Exp Ophthalmol.* 2005;33(3):252-258. [CrossRef]
57. Kalinina Ayuso V, van de Winkel EL, Rothova A, de Boer JH. Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. *Am J Ophthalmol.* 2011;151(2):217-222. [CrossRef]
58. Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. *N Engl J Med.* 2017;376(17):1637-1646. [CrossRef]
59. Quartier P, Baptiste A, Despert V, et al. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. *Ann Rheum Dis.* 2018;77(7):1003-1011. [CrossRef]
60. Roberts JE, Nigrovic PA, Lo MS, Chang MH. Weekly adalimumab, an effective alternative for refractory uveitis in children. *J Clin Rheumatol.* 2022;28(1):e301-e304. [CrossRef]
61. Correll CK, Bullock DR, Cafferty RM, Vehe RK. Safety of weekly adalimumab in the treatment of juvenile idiopathic arthritis and pediatric chronic uveitis. *Clin Rheumatol.* 2018;37(2):549-553. [CrossRef]
62. Kouwenberg CV, Koopman-Kalinina Ayuso V, de Boer JH. Clinical benefits and potential risks of adalimumab in non-JIA chronic paediatric uveitis. *Acta Ophthalmol.* 2022;100(4):e994-e1001. [CrossRef]
63. Ozdemir HB, Ozdal PC. Clinical characteristics and treatment of pars planitis: an adalimumab experience. *Graefes Arch Clin Exp Ophthalmol.* 2022;260(2):561-569. [CrossRef]
64. Song H, Zhao C, Xiao J, Gao F, Li D, Zhang M. The efficacy and safety of adalimumab in treating pediatric noninfectious chronic anterior uveitis with peripheral retinal vascular leakage: a pilot study. *Front Med (Lausanne).* 2022;9:813696. [CrossRef]
65. Norcia LF, Kiappe OP, Jorge EC. Biological therapy in noninfectious pediatric uveitis: a systematic review. *Clin Ophthalmol.* 2021;15:3765-3776. [CrossRef]
66. Tugal-Tutkun I, Ayranci O, Kasapcopur O, Kir N. Retrospective analysis of children with uveitis treated with infliximab. *J AAPOS.* 2008;12(6):611-613. [CrossRef]
67. Miraldi Utz V, Bulas S, Lopper S, et al. Effectiveness of long-term infliximab use and impact of treatment adherence on disease control in refractory, non-infectious pediatric uveitis. *Pediatr Rheumatol Online J.* 2019;17(1):79. [CrossRef]
68. Lanz S, Seidel G, Skrabl-Baumgartner A. Golimumab in juvenile idiopathic arthritis-associated uveitis unresponsive to adalimumab. *Pediatr Rheumatol Online J.* 2021;19(1):132. [CrossRef]
69. Miraldi Utz V, Angeles-Han ST, Mwase N, et al. Alternative biologic therapy in children failing conventional TNFα inhibitors for refractory, noninfectious, chronic anterior uveitis. *Am J Ophthalmol.* 2022;244:183-195. [CrossRef]
70. Gaggiano C, Rigante D, Tosi GM, et al. Treating juvenile idiopathic arthritis (JIA)-related uveitis beyond TNF-α inhibition: a narrative review. *Clin Rheumatol.* 2020;39(2):327-337. [CrossRef]
71. Ramanan AV, Dick AD, Guly C, et al. Tocilizumab in patients with anti-TNF refractory juvenile idiopathic arthritis-associated uveitis (APTITUDE): a multicentre, single-arm, phase 2 trial. *Lancet Rheumatol.* 2020;2(3):e135-e141. [CrossRef]
72. Lerman MA, Lewen MD, Kempen JH, Mills MD. Uveitis reactivation in children treated with tumor necrosis factor alpha inhibitors. *Am J Ophthalmol.* 2015;160(1):193-200.e1. [CrossRef]
73. Acharya NR, Patel S, Homayounfar G, et al. Relapse of juvenile idiopathic arthritis-associated uveitis after discontinuation of immunomodulatory therapy. *Ocul Immunol Inflammm.* 2019;27(4):686-692. [CrossRef]
74. Acharya NR, Ebert CD, Kelly NK, et al. Discontinuing adalimumab in patients with controlled juvenile idiopathic arthritis-associated uveitis (ADJUST-adalimumab in Juvenile Idiopathic Arthritis-associated uveitis Stopping Trial): study protocol for a randomised controlled trial. *Trials.* 2020;21(1):887. [CrossRef]
75. Ramanan AV, Guly CM, Keller SY, et al. Clinical effectiveness and safety of baricitinib for the treatment of juvenile idiopathic arthritis-associated uveitis or chronic anterior antinuclear antibody-positive uveitis: study protocol for an open-label, adalimumab active-controlled phase 3 clinical trial (JUVE-Bright). *Trials.* 2021;22(1):689. [CrossRef]
76. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and treatment of juvenile idiopathic arthritis-associated uveitis. *Arthritis Care Res (Hoboken).* 2019;71(6):703-716. [CrossRef]
77. Angeles-Han ST, Lo MS, Henderson LA, et al. Childhood Arthritis and Rheumatology Research Alliance Consensus treatment plans for juvenile idiopathic arthritis-associated and idiopathic chronic anterior uveitis. *Arthritis Care Res (Hoboken).* 2019;71(4):482-491. [CrossRef]
78. Constantin T, Foeldvari I, Anton J, et al. Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. *Ann Rheum Dis.* 2018;77(8):1107-1117. [CrossRef]