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REVIEW

Challenges of Childhood Uveitis

Reem Abdwani

تحديات التِهاب العِنَبِيَّة في الطفولة

ريم عبدواني

الملخص: الْتِهابُ العِنَبِيَّة المزمن مرض نادر لكنه يمكن أن يهدد سلامة البصر. السبب الأكثر انتشارا لالْتِهابُ العِنَبِيَّة المزمن غير المعدي هو الالتهاب غير معروف السبب. بعض أمراض أجهزة الجسم في الطفولة يمكن أن يصاحبها الْتِهابُ العِنَبِيَّة وهذا ما سنناقشه هنا. إذ إن ذلك يستحق عناية خاصة. الفروقات الفريدة في الأطفال تم توضيحها مع اعتبارات هامة في التحديات التي تحصل في التشخيص والعلاج. بينما تبقى الستيرويدات القشرية الدعامة الأساسية في العلاج الأولي. لكن هناك عدد كبير من العوامل الكابتة للمناعة استعملت مع نجاحات متفاوتة. تم مراجعة دور بعض العوامل مثل الميثوتركسيت والسايكلوسبورين وبعض العوامل الحيوية الجديدة مثل ايتانسيبت وانفليكسيماب واديلموماب. يمكن الحصول على نتائج ناجحة بواسطة العلاج بالعوامل الكابتة للمناعة عندما تعطى في بداية المرض. ولو أن القضية بحاجة إلى دراسات سريرية لمعرفة وتحديد فعالية هذه الإستراتيجية.

مفتاح الكلمات: الْتِهابُ العِنَبِيَّة. العلاج.

ABSTRACT: Chronic uveitis is a rare, but potentially sight-threatening disease. The most common cause of chronic non-infectious uveitis is "idiopathic uveitis". However, some systemic diseases are associated with chronic uveitis in children and are discussed. Chronic uveitis merits special consideration in children. The unique differences in children are highlighted with special consideration for the diagnostic and therapeutic challenges encountered in their management. While corticosteroids remain the mainstay of initial therapy, a wide range of immunosuppressive agents have been used with variable success. The role of immonomodulatory agents such as methotrexate, cyclosproin and some of the new biologic agents such as etanecept, infliximab, adalimumab are reviewed. Successful outcomes may be achieved with appropriate immunosuppressant therapy when given early in the disease, although clinical trials are required to define the true efficacy of this strategy.

Keywords: Uveitis; Treatment

Children are not miniature adults so there are differences between childhood and adult onset uveitis. Special considerations and modifications are required in our approach to dealing with childhood uveitis. The most common aetiologies, the disease presentation, clinical course and outcome are quite different in children compared to adults. In general, idiopathic uveitis is the most common cause of uveitis; however, the most common identifiable cause of uveitis in adults and children varies. In adults, the most common identifiable cause of uveitis is HLA-B27 associated spondyloarthropathy, while in children the most common identifiable cause is juvenile idiopathic arthritis. Similarly, the clinical presentation is quite different between the two. In adults, the most common presentation of uveitis is an acutely painful red eye, while in children it is chronic, bilateral persistent uveitis and can be completely asymptomatic; therefore, the diagnosis of uveitis is often delayed in children because it goes unrecognised or misdiagnosed. Another major difference between children and adults is that the prognosis of uveitis is usually worse in children, with up to 35% of children experiencing complications such as posterior synechiae, cataract, band keratopathy, glaucoma and visual impairment. Similarly, even when complications, such as glaucoma, develop secondary to uveitis in both adults and children, they tend to be more severe in children than in adults.[1]

Another special consideration in children with chronic uveitis, which adds to the diagnostic and therapeutic challenges, is the unique clinical presentations of the disease in children, such as leukocoria, strabismus, or difficulty with routine activities at home or at school. Similarly, children have unique complications due to uveitis that are not seen in adults, such as the risk of developing amylopia and strabismus. Another challenge in children is the difficulty of routine examination. Complete examination is essential

Department of Child Health, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman
Email: reemabd@hotmail.com

Table 1: Infectious causes of uveitis

Bacterial	Viral	Fungal	Parasitic
Tuberculosis	Cytomegalovirus	Aspergillosis	Toxocariasis
Atypical mycobacteria	Epstein-Barr	Blastomycosis	Toxoplasmosis
Brucellosis	Herpes simplex	Candidiasis	*Pneumocystis carinii*
Syphilis	Herpes zoster	Coccidioidomycosis	
Lyme disease	Herpes zoster	Cryptococosis	
Cat scratch disease	Mumps	Histoplasmosis	
	Rubeola		
	HIV		

and often requires examination under anaesthesia. Additionally, children are more vulnerable than adults and have different sides effects to systemic therapy such as corticosteroid-induced growth retardation in prepubescent children and an increased tendency for corticosteroids to induce ocular hypertension and cataracts.[2]

Definition and Classification of Uveitis

Uveitis is inflammation of the uvea, the middle coat of the eye that is sandwiched between the sclera and retina. The ophthalmologist is uniquely placed to observe directly the amount of inflammation and measure the eye's ability to function (visual acuity and visual field). Clinically, the patient could present with pain, redness, headache, photophobia and change in vision. However, the patient can also be entirely asymptomatic in cases of chronic uveitis.

Uveitis is classified according to different categories. The classification of uveitis can be based on anatomical location as recommended by the International Uveitis Study Group (IUSG).[1] Anterior uveitis refers to inflammation of the anterior chamber including iritis, iridocyclitis, and anterior cyclitis. Intermediate uveitis involves the vitreous including *pars planitis*, posterior cyclitis and hyalitis, while posterior retinitis involves the retina and choroids including choroiditis, chorioretinitis and neuroretinitis. The term panuveitis describes a uveitis that involves the anterior chamber, the retina and the choroids. Uveitis can also be classified as acute, recurrent or chronic based on the onset and duration of inflammation. In addition, uveitis can be classified as either infectious or non-infectious in aetiology and by the presence or absence of any systemic disease.

Epidemiology

Uveitis commonly affects young adults; however, it occurs in all age groups from children to the elderly. In general, uveitis is an uncommon disease with an annual incidence of 17-52/100,000 population.[2,3] In children, uveitis is rare with an annual incidence of 4-7/100,000 children/year.[4,5] Children constitute 5-10% of all cases of uveitis seen in many tertiary centres,[6] but more recently a higher percentage (33%) of childhood uveitis has been reported.[7] A recent study of the prevalence of uveitis in an urban population in South India, found evidence of either past or active uveitis in 1 out of 140 people in the population, suggesting that the prevalence of uveitis may be of higher magnitude in developing than in developed nations.[8]

Aetiology of Uveitis

There is a wide range of differential diagnoses in uveitis. The role of the physician is to make sure that the patient does not have an infectious cause of uveitis before considering a systemic non-infectious cause. Table 1 lists bacterial, viral, spirochetal, fungal and parasitic causes of uveitis. In children, it is also very important to rule out masquerading syndromes that may mimic uveitis such as malignancies, leukaemia, lymphoma or neuroblastoma. Once infectious and masquerading syndromes have been excluded, one can then consider non-infectious systemic conditions [Table 2]. However, the most common cause of uveitis in both adults and children still remains "idiopathic uveitis".[3]

Given the diversity of differential diagnoses, there

Table 2: Systemic inflammatory non-infectious causes of uveitis

Chronic inflammatory diseases
Juvenile idiopathic arthritis
Reactive arthritis
Ulcerative colitis
Crohn's disease
Systemic connective tissue diseases
Systemic lupus erythematosus
Sjögren's syndrome
Systemic Vasculitis
Behçet's disease
Sarcoidosis
Wegener's granulomatosis
Polyarteritis nodosa
Kawasaki disease
Relapsing polychondritis
Others
Tubulointerstitial nephritis uveitis syndrome
Blau syndrome
Vogt-Koyanagi-Harada syndrome

is no recommended routine battery of investigations for the work-up of uveitis. The most helpful test in raising the diagnostic probability is a proper history and physical examination. In children, the history is often limited; therefore, information obtained from parents is valuable. Similarly, examination may be difficult due to poor cooperation from the child and subtle ocular findings so examination under anesthaesia may be necessary to complete the assessment. Appropriate investigations need to be tailored to individual cases, depending upon the history and physical examination findings, in order to support the clinical suspicion.

Systemic Inflammatory Non-Infectious Causes of Uveitis

Uveitis can occur as a manifestation in many systemic diseases [Table 2]. Some of these systemic diseases occurring in the paediatric age group will be discussed.

JUVENILE IDIOPATHIC ARTHRITIS (JIA)

JIA is defined as chronic arthritis of unknown aetiology occurring before the age of 16 years and lasting at least six weeks. The international league against rheumatism (ILAR) classification of JIA includes seven subtypes:systemic onset JIA, oligoarticular JIA, polyarticular rheumatoid factor (RF) positive and negative JIA, enthesitis-related arthritis, juvenile psoriatric arthritis and unclassified JIA.[9]

The uveitis affecting children with JIA is predominantly bilateral chronic anterior, non-granulomatous uveitis. It is important to note that, although the disease can cause macular oedema as a complication, the presence of features of posterior uveitis (choroidal infiltrate, retinitis, retinal vasculaitis) is not consistent with the diagnosis of JIA associated uveitis; if found, an alternative diagnosis should be considered.

JIA associated uveitis is especially common in young girls who have oligoarticular JIA, present with early disease onset and are anti-nuclear antibody (ANA) seropositive.[10] In patients with oligoarticular JIA, uveitis is observed in 16-40% of cases, while in RF negative polyarticular JIA, uveitis is observed in 5-24% of cases and in 2-23% of patients with psoriatic arthritis; however, uveitis is uncommon in RF positive polyarticular JIA and in systemic onset JIA.[11-14]

Uveitis precedes arthritis in 10% of cases; however, most children develop uveitis within 4 to 7 years of the onset of arthritis, although the risk is never entirely absent.[15] The onset is often entirely asymptomatic in chronic uveitis; therefore, early detection by slit lamp examination should be performed at the time of diagnosis in every child with uveitis and repeated at regular intervals as suggested by the American Academy of Pediatrics [Table 3].[16]

BEHÇET'S DISEASE

Behçet's Disease (BD) is a multisystem inflammatory disorder characterised by a triad of recurrent oral ulcers, genital ulcers and uveitis; but many systems may be involved including the skin, joints, central nervous system and gastrointestinal tract, with vascular inflammation predisposing to thrombosis as a prominent feature. In Asian and Middle Eastern populations, in whom the disease is most prevalent, HLA-B51 is a marker for BD. Ocular involvement occurs in 30-61% of children with BD.[17-19] It is typically bilaterally episodic, involves the entire uveal tract (panuveitis), and may not resolve completely between episodes. Hypopyon,

Table 3: Guidelines for ophthalmologic screening in juvenile idiopathic arthritis (JIA)

JIA sub-type	Age < 7 years at onset	Age >7 years at onset
Oligoarticular JIA		
+ ANA	H	M
- ANA	M	M
Polyarticular JIA		
+ ANA	H	M
- ANA	M	M
Systemic JIA	L	L

Legend: *ANA = anti-nuclear antibody; H = high risk (ophthalmologic exam every 3 months); M = medium risk (ophthalmologic exam every 6 months); L = low risk (ophthalmologic exam every 12 months)*

a severe anterior uveitis with purulent material in the anterior chamber, is characteristically seen in patients with Behçet's disease. Other ocular involvement includes retinal vasculitis and optic neuritis. In BD uveitis there is high frequency of blindness in untreated patients.

SARCOIDOSIS

Sarcoidosis is a multisystem disorder characterised pathologically by the presence of noncaseating granulomas in the involved organs. Two subsets of paediatric sarcoidosis are identified. The 8-15 year old group develops disease similar to adults, characterised by pulmonary reticular opacities, and hilar lymphadenopathy with skin, joint or eye involvement. Younger children, however, are characterised by a triad of skin rash, arthritis and uveitis without apparent lung involvement or lymphadenopathy. Uveitis may be more common in early onset disease than in the later onset disease. In children in the 8-15 year old group, 32% had ocular disease,[20] while in the early onset sarcoidosis 77% of children had ocular disease.[21] Ocular involvement in sarcoidosis, unlike JIA, can involve all segments of the eye including anterior uveitis, posterior uveitis, retinal vasculitis and kerato-conjunctivitis. In addition, extraocular orbital tissue involvement can occur, affecting the lacrimal glands, extraocular muscles and optic nerve sheath, and may present as a soft tissue orbital mass. Anterior uveitis is the most common paediatric ocular involvement in sarcoidosis.[22]

BLAU SYNDROME

Blau syndrome (BS) is a multisystem granulomatous disease. BS and early onset sarcoidosis are now believed to belong to the same disease spectrum. BS represents a familial autosomal dominant form while early onset sarcoidosis represents a sporadic form. It is characterised by inflammation of the skin, eye and joints, with a typical onset before 5 years**.** Both BS and early onset sarcoidosis are associated with mutations in the gene encoding NOD2/CARD15 located on chromosome 16.[23] Diagnosis may be confirmed through skin, synovial or conjunctival biopsy as well as by genetic testing.

TUBULOINTERSTITIAL NEPHRITIS AND UVEITIS SYNDROME

Tubulointerstitial nephritis and uveitis syndrome (TINU) is a rare oculo-inflammatory disease which is comprised of acute idiopathic tubulointerstitial nephritis and uveitis. TINU may be associated with other systemic findings including fever, weight loss, fatigue, malaise, anorexia, arthralgia, myalgia and headache. Uveitis is predominantly anterior although posterior uveitis can occur. Uveitis is typically bilateral, although unilateral or alternating uveitis has been observed. TINU occurs in all age spectrums, but most commonly in adolescent females with favorable prognosis.[24] Nephritis tends to be self-limiting, whereas uveitis tends to relapse and recurrences tend to be more severe than the initial uveitis. Therefore, routine careful ophthalmologic examinations are required to prevent secondary ocular complications.

VOGT-KOYANAGI-HARADA SYNDROME

Vogt-Koyanagi-Harada (VKH) syndrome is a rare systemic disease involving various melanocyte-containing organs. This syndrome is characterised by bilateral granulomatous panuveitis associated

with a variety of extra-ocular manifestations including central nervous system, auditory and integumentary system involvement. VKH syndrome is an immune-mediated disease. The mechanism of the disease is thought to be a T helper cell mediated autoimmune attack of melanocytes in the skin, uvea, central nervous system and inner ear. The American Uveitis Society has recommended that at least three of the following four criteria be met to confirm the diagnosis of VKH syndrome: 1) bilateral iridocyclitis; 2) posterior uveitis; 3) cerebrospinal fluid (CSF) pleocytosis or evidence of tinnitus, dysacusis, headache or meningismus, or cranial nerve involvement and 4) cutaneous findings of vitiligo, alopecia, or poliosis. VKH associated uveitis tends to be more aggressive in children than in adults.[25]

Local Treatment of Uveitis

Treatment of uveitis in children is challenging. The outcome of uveitis is often poor with up to 35% of children with uveitis left with vision loss as a result of complications.[6] There are a number of reasons that lead to the poor outcome of uveitis in children including: 1) delay in diagnosis, as the majority of paediatric patients are practically asymptomatic; 2) a more severe and aggressive course than in adults; 3) poor compliance with therapy. Another reason that makes effective treatment challenging is that there are only limited numbers of randomised controlled clinical trials that can guide therapy in paediatric uveitis based on evidence-based practice. Most of the paediatric literature in the treatment of systemic diseases associated with uveitis is based on small retrospective case series. Treatment with immunosuppressive agents should be initiated once infectious and masquerading causes have been excluded and in conjunction with a paediatric rheumatologist who has experience in prescribing and in monitoring for drug toxicity.

Treatment is often initiated by an ophthalmologist once the diagnosis of uveitis is made. Regardless of the cause, initial treatment of anterior uveitis begins with corticosteroids eye drops that effectively penetrate the cornea and have a highly potent anti-inflammatory effect. Prednisolone actetate 1% is often the drug of choice. Frequency of administration, which could be up to hourly administration, depends on the intensity of the inflammatory reaction; however, frequency is tapered once the inflammation improves. Careful and frequent review is necessary to avoid excessive use of topical steroids which increases the risk of medication-related side-effects including glaucoma, cataract and increased susceptibility to eye infections, including reactivation of latent herpetic infections. Similarly, early withdrawal of topical corticosteroids may lead to rebound ocular inflammation. In addition to topical corticosteroids, a topical mydriatic agent such as 1% cyclopentolate is often initiated in the treatment of uveitis. This gives rapid relief of pain that may be caused by uveal smooth muscle spasm and may prevent the formation of synechia. Periocular injections of steroids can be considered in patients with intermediate and posterior uveitis to achieve rapid quiescence of inflammation as part of the short-term management to prevent disease exacerbation.

Following local treatment for uveitis (corticosteroids and mydriatic agents) therapy should be escalated in the following circumstances: 1) the uveitis is refractory to treatment with topical steroids; 2) the requirement of unacceptably high doses of steroids for a prolonged period to control uveitis; 3) the development of unacceptable side-effects. In these situations, the introduction of immunosuppressive agents is warranted. The current trend is for earlier and more aggressive use of immunosuppressive agents. The traditional approach of waiting until vision drops or complications develop before beginning immunmodulatory therapy is no longer considered appropriate.

Systemic Treatment of Uveitis

SYSTEMIC CORTICOSTEROIDS

Glucocorticoids (oral/parenteral route) are the most potent anti-inflammatory agents. The dose of steroids needed to control inflammation varies according to extent of uveitis. It may be as low as 2-4mg/day and as high as requiring pulses of methylprednisolone 30mg/kg/day. Glucocorticoids are very effective in achieving a very rapid control over inflammation; however, their side-effects make them our foe. Some of these include Cushing's syndrome, growth suppression, osteoporosis,

avascular necrosis, hypertension, myopathy, increased risk of infection, glucose intolerance and adrenal crisis. Due to the severity of potential side-effects of glucocorticoids, other immunosuppressive agents have been used for the treatment of uveitis.

METHOTREXATE

Methotrexate is one of the most commonly used immunosuppressive agents due to its low cost and well-known safety profile. Its once weekly dose enables increased compliance. The general recommended dose for methotrexate in the paediatric age group is 10-25 mg/m^2 given orally or parenterally. It is generally well-tolerated; however, some of the most encountered side-effects include gastrointestinal toxicity in the form of nausea, vomiting and abdominal pain. Switching the route of administration of the drug from the oral to the parenteral route as well as folic acid supplementation may help overcome the gastrointestinal toxicity. Other side-effects include mucositis, increased risk of opportunistic infections, haematologic toxicity (pancytopenia), hepatic toxicity and interstitial pneumonitis. Concern about methotrexate's teratogenic effect is considered in the later stages of life. Recommended routine laboratory monitoring for methotrexate toxicity includes complete blood count and liver function tests at 4-6 weekly intervals. Some of the main reasons for the elevated liver enzymes on routine screening are the drawing of blood within two days of taking the medication or the presence of an intercurrent viral illness. Generally speaking, liver enzymes normalise with a decrease in the methotrexate dose or transient discontinuation.

A number of studies have demonstrated the effective use of methotrexate in the treatment of paediatric uveitis due to a variety of systemic inflammatory conditions.[26-29] Heiligenhaus *et al.* treated 35 patients with JIA with methotrexate for an associated anterior uveitis.[26] A total of 71% of patients were able to achieve remission with methotrexate alone, while 20% of patients required the addition of another immunosuppressive agent to achieve quiescence of uveitis. Shetty *et al.* successfully used methotrexate in the treatment of uveitis associated with sarcoidosis in two children.[27] Soheilian *et al.* treated ten patients with paediatric VHK-associated panuveitis with oral prednisolone with methotrexate being added for six refractory patients. In all the eyes of these patients, inflammation decreased and vision was preserved or improved.[28] Similarly, methotrexate has been found to be effective in the treatment of TINU syndrome.[29]

CYCLOSPORINE

Cyclosporine (CsA) is a fungal analogue that inhibits T-cell activity by inhibiting the translocation of a family of transcription factors leading to reduced transcriptional activation of several cytokines including IL-2 IL-3, IL-4, G-CSF, and interferon-gamma. The usual dose for CsA for the treatment of uveitis is 3-5mg/kg.

Some of the common side effects of CsA include impaired renal function, hypertension, hepatic toxicity, gum hyperplasia and hypertrichosis. Another serious complication includes neurotoxicity in the form of headaches, parasthaesia and seizures. Concomitant use of non-steroidal anti-inflammatory drugs may exacerbate these toxic effects. It is important to monitor closely for renal toxicity that can occur at the initiation of therapy. The recommendation is to monitor for drug toxicity by monitoring blood pressure and carrying out a renal function test biweekly at the start of the treatment and then on a monthly basis. A rise in serum creatinine of 30%, despite being in the normal reference creatinine range, is considered to be significant and merits dose reduction. Complete blood count and liver function tests should be monitored on a monthly basis as well.

There are many controversial studies in the literature on the efficacy of CsA in the treatment of chronic uveitis in children. Kilmartin *et al*. used low dose CsA in the treatment of refractory non-infectious uveitis in 14 patients (n = 25 eyes) for a mean duration of 20.9 months (range 3.5-88.3 months). In their cohort of patients, visual acuity improved or was maintained in 92% of eyes and the binocular indirect ophthalmoscopy (BIO) score improved in 75% of eyes, indicating that CsA is safe and effective in the treatment of refractory non-infectious uveitis in childhood.[30] However, the results of both Walton et al. and Tappeiner *et al*. did not support the effective use of CsA in the treatment of chronic uveitis in children.[31,32] Walton *et al*. treated 15 children with chronic uveitis using higher doses of CsA in combination with prednisolone. After 4 years of treatment, 4 patients discontinued

medication as they were in remission, 2 patients discontinued medication due to treatment failure or side-effects and 9 patients continued to be on CsA with ongoing median vitreous inflammation of 0.5. Tappeiner *et al*. used low dose CsA in 82 children with JIA associated chronic uveitis. When CsA was used as a monotherapy, the uveitis became inactive in 24% of cases. However, when CsA was used in combination with other immunosuppressive agents for the treatment of uveitis, inactivity occurred in 48.6% (p = 0.037). Pre-existing cystoid macular oedema did not resolve under CsA treatment in any of the patients. CsA was discontinued in 11% of cases due to systemic side-effects. Tappeiner *et al*. concluded that CsA has limited value in the treatment of JIA associated uveitis.

There are other immunosuppressive agents like azathioprin, mycophenolate mofetil and cyclophosphomide that are used in other types of paediatric inflammatory disease and have been used in the treatment of uveitis in children. However, there is scant published data on the use of these agents in the paediatric literature.

BIOLOGIC AGENTS

Biologic agents have successfully been introduced in the treatment of many autoimmune conditions including uveitis. Tumour necrosis factor (TNF) alpha is persistently elevated in the aqueous humour and in the peripheral blood in patients with chronic uveitis.[33] This cytokine is thought to participate actively in the pathogenesis of the inflammatory process in uveitis; however, its role is still unclear. There are three different types of anti-TNF antagonists which include etanercept, infliximab, and adalimumab. One has to be aware of the problems associated with the use of these agents, some of which include an increased risk of developing opportunistic infections, malignancy and demyelinating diseases.[34]

Etanercept, a soluble TNF receptor, is a fusion protein made up of two recombinant p75-soluble receptors fused with the Fc fragment from human IgG. The Fc fragment is added to prolong its half-life. It is administered subcutaneously at a dose of 0.4mg/kg twice weekly. No spectacular successes have been reported in the literature on the use of etanercept in the treatment of uveitis. Smith *et al*. reported a worsening of anterior uveitis and the development of a new onset of scleritis in patients, even though the systemic inflammatory disease was brought under control.[35] Similarly, Foster *et al*. found no difference in the relapse rate and the final visual acuity in a randomised double-blinded placebo controlled trial using etanercept in the treatment of chronic uveitis in 20 children.[36] Although Reiff *et al*. notice marked significant improvement of uveitis within 3 months in 10 children with JIA associated uveitis, on follow-up only 4 patients had a sustained response.[37]

Infliximab is a chimeric monoclonocal antibody; the term "chimeric" refers to the use of both murine and human components in the drug. It blocks the action of the pro-inflammatory TNF alpha by binding to it and preventing it from signalling the receptors on the surface of cells. The results have been more promising with infliximab than with etanercept. Saurenmann *et al*. treated 21 children with chronic uveitis with the anti-TNF agents etanercept (n = 11) and infliximab (n = 13) resulting in 24 treatment courses.[38] The response to etanercept treatment was good in 27%, moderate in 27% and poor in 45% of the patients, whereas the response to infliximab treatment was good in 38%, moderate in 54% and poor in 8% of patients. The difference in the percentage of patients with a moderate or good response was statistically significant (p = 0.0481). A lower rate of complications was observed in the infliximab-treated group. Similarly, Galor *et al*. performed a retrospective analysis on 22 patients treated with anti-TNF therapy, comparing the effectiveness of etanercept versus infliximab in the treatment of ocular inflammation.[39] They reported a statistically significant difference in the reduction of the inflammation recurrence rate, topical steroid use and treatment response in patients treated with infliximab compared to those treated with etanercept. Whilst there was an initial response in patients treated with etanercept, all eventually required a change in medication to control inflammation.

Adalimumab is a fully human monoclonal antibody that binds to TNFα, preventing it from activating TNF receptors and therefore down regulates inflammatory reactions. The results in the literature on the treatment of chronic uveitis in children with adalimumab have been encouraging even in patients who are non-responsive to other anti-TNF agents. Biester *et al*. described an improvement of uveitis in 88% of the patients

when their response was based on the number of relapses.[40] Vazquez-Cobian *et al.* showed improved activity in 81% of the eyes.[41] In another retrospective observational study of 20 patients with JIA associated chronic uveitis treated with adalimumab, 35% of patients showed improved ocular inflammation especially in patients who were younger and had shorter disease duration.[42] Differences in patient characteristics and response criteria may explain the lower rate of favorable outcomes in the last study compared with previous studies. There is also favorable evidence that supports switching biologic agents when there is loss of initial clinical response to one biological agent (infliximab or adalimumab). Switching biologic agents can restore control of intraocular inflammation. In addition, switching helps to control systemic symptoms and allows ease of administration.[43]

Daclizumab is a recombinant humanised immunoglobulin G monoclocal antibody that acts as an IL-2 receptor antagonist. IL-2 receptors are expressed on activated T-cell surfaces during inflammation, antagonising the receptor and preventing T-cell proliferation and differentiation. In a recent open-label prospective study, 6 patients with JIA associated uveitis were treated with high dose intravenous daclizumab for 52 weeks. Four of the 6 participants achieved two-step reduction in anterior chamber cells according to the Standardization of Uveitis Nomenclature Working Group grading scheme for anterior chamber cells 12 weeks into the study and met the primary efficacy endpoint. One additional patient responded to reinduction, whereas one patient failed reinduction and was considered an ocular treatment failure.[44] In the literature on adults, daclizumab appears to be relatively well tolerated and may be promising in the treatment of ocular inflammatory disorders.[45,46]

Interferon (alpha) is a cytokine that disrupts viral replication, prevents tumour growth, acts against tolerance inducers of autoimmune disease and has an antiproliferative and apoptotic effect on T-cells. In inflammatory eye disease, interferon (alpha) has been mainly used in the treatment of uveitis associated with Behçet's disease.[47,48] In the paediatric literature, there is one report of its use in children with uveitis: a retrospective study of 7 children with corticodependent uveitis of Behcet's disease who were treated with interferon (alpha). A remarkable corticosparing effect with remission maintenance was achieved in five out of seven patients. The remission was sustained in four of the five patients even after interferon was discontinued in three of them. The other patient relapsed 1.5 yrs after the discontinuation of interferon. Two patients faced early severe adverse events: thrombosis and major depression.[49]

Other biologic therapies that are used in the treatment of rheumatic diseases are rituximab (anti-B cell therapy), and alemtuzumab, a humanised monoclonal antibody that acts against the pan-lymphocyte antigen CD52, anti-interleukin 6 antibodies and anti-cytotoxic T-lymphocyte associated antigens (CTLA-4). The use of these agents in the treatment of ocular inflammatory conditions is still being explored. Besides medical treatment, surgery has a prominent role in the management of complications secondary to chronic uveitis such as cataract, glaucoma, and vitroretinal problems. Surgical interventions are complicated and beyond the scope of this review.

Conclusion

There are many diagnostic and therapeutic challenges that we need to overcome when dealing with children with chronic uveitis. A close relationship should be fostered between paediatricians, paediatric rheumatologists and ophthalmologists for the effective monitoring of these patients who have multiple medical, surgical and refractive needs. The longer the uveitis is under treated, the worse seem to be the complications in frequency and severity. Given the relatively poor prognosis, early and aggressive treatment with immunosuppressive agents and, in more severe cases, biologic agents is advocated. Experience in treating adult uveitis cannot necessarily be extrapolated to paediatric uveitis. Given the rarity of the disease, multi-centred randomised controlled trials are required to determine the long term efficacy, safety and optimal dosing of various therapeutic agents in children.

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