Uveitis associated with juvenile idiopathic arthritis

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Abstract | Uveitis is a potentially sight-threatening complication of juvenile idiopathic arthritis (JIA). JIA-associated uveitis is recognized to have an autoimmune aetiology characterized by activation of $CD4^+$ T cells, but the underlying mechanisms might overlap with those of autoinflammatory conditions involving activation of innate immunity. As no animal model recapitulates all the features of JIA-associated uveitis, questions remain regarding its pathogenesis. The most common form of JIA-associated uveitis is chronic anterior uveitis, which is usually asymptomatic initially. Effective screening is, therefore, essential to detect early disease and commence treatment before the development of visually disabling complications, such as cataracts, glaucoma, band keratopathy and cystoid macular oedema. Complications can result from uncontrolled intraocular inflammation as well as from its treatment, particularly prolonged use of high-dose topical corticosteroids. Accumulating evidence supports the early introduction of systemic immunosuppressive drugs, such as methotrexate, as steroid-sparing agents. Prospective randomized controlled trials of TNF inhibitors and other biologic therapies are underway or planned. Future research should aim to identify biomarkers to predict which children are at high risk of developing JIA-associated uveitis or have a poor prognosis. Such biomarkers could help to ensure that patients receive earlier interventions and more-potent therapy, with the ultimate aim of reducing loss of vision and ocular morbidity.

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Introduction

Uveitis (inflammation of the uveal components of the eye, namely the iris, choroid and retina) is the most common extra-articular complication of juvenile idiopathic arthritis (JIA). However, the biological basis of the association between arthritis and uveitis in JIA is poorly understood.[1] Uveitis is classified according to the involved anatomy and the time course of disease, as defined by the Standardization of Uveitis Nomenclature (SUN) international working group.[2,3] Anatomically, uveitis can be described as anterior, intermediate, posterior or panuveitis (Figure 1). The temporal pattern is classified as acute, subacute, chronic or recurrent. The most common form of eye inflammation associated with JIA is chronic anterior uveitis, which can be unilateral or bilateral. Acute anterior uveitis can also occur in JIA, and is usually associated with enthesitis-related arthritis and HLA-B27 positivity. If inadequately treated, uveitis can lead to ocular complications, including cataracts, glaucoma, band keratopathy and persistent cystoid macular oedema, and can ultimately result in visual impairment and blindness.[4]

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A.D.D. declares that he has served as a consultant for Abbvie, Genentech and Novartis, has received grants from Novartis, and is a co-investigator for the SYCAMORE trial of adalimumab in patients with JIA-associated uveitis, which is funded by Health Technology Assessment and Arthritis Research UK. A.V.R. declares that he has received honoraria or speaker's fees from Abbvie, Novartis, Pfizer, Roche, and Swedish Orphan Biovitrum Pharmaceuticals, and that he is co-chief investigator of the SYCAMORE trial. E.S.S. declares no competing interests.

In this article, we discuss the epidemiology, assessment and management of JIA-associated uveitis. We focus on the immunopathogenesis of this disorder and describe the potential for biomarkers to improve its treatment.

Epidemiology

The reported prevalence of uveitis among children with JIA varies from 11.6%[5] to 30%.[6] The prevalence of uveitis is increased in female patients, those with a young age (<6 years) at onset of arthritis, and in some categories of JIA—being most frequent in oligoarticular disease (affecting four or fewer joints within the first 6 months after disease onset) and in patients who are positive for antinuclear antibodies (ANAs).[4,7,8] Several retrospective studies have confirmed strong associations between uveitis and some of these factors, although not all studies confirmed associations with all four factors.[9–11] These risk factors are probably not independent of each other; in a retrospective study of 1,047 patients with JIA, the risk of developing uveitis was age-dependent in girls, but not in boys.[12]

In another study of 1,081 patients with JIA, 13.1% of whom developed uveitis, chronic anterior disease was the most frequent type (68.3%), followed by acute anterior disease (16.2%), recurrent anterior disease (12%) and panuveitis (3.5%).[13] The mean time between diagnosis of JIA and uveitis onset was 1.8 years, although this interval was significantly shorter in patients with uveitis who developed ocular complications than in those who

Key points

- Uveitis affects 11–30% of children with juvenile idiopathic arthritis (JIA)
- Chronic anterior uveitis is usually asymptomatic initially but can lead to visually disabling complications; therefore, screening is essential
- Initial treatment is with topical corticosteroids but evidence supports the early introduction of systemic immunosuppressive drugs, such as methotrexate, as steroid-sparing agents
- Prospective controlled studies of biologic therapies, including adalimumab and tocilizumab, are underway or planned
- Future research to investigate the pathogenesis of JIA-associated uveitis and identify novel biomarkers could enable earlier diagnosis and more-effective treatment

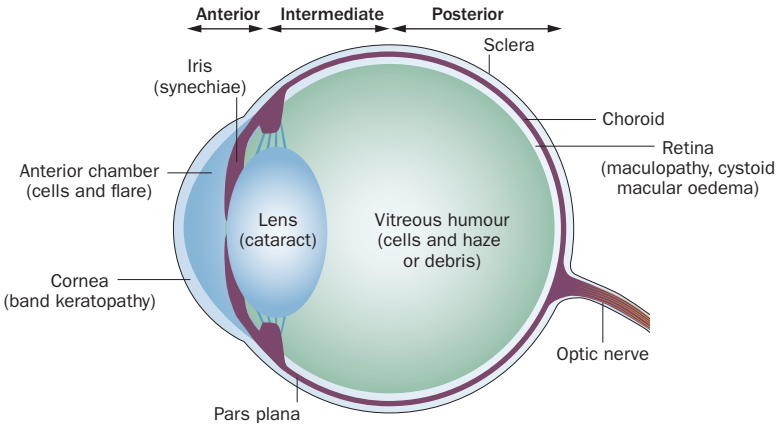

Figure 1 | Cross-section of eye showing areas affected in anterior, intermediate and posterior uveitis. Potential ocular complications are listed in brackets. Permission obtained from Wiley © Hughes, E.H. & Dick, A.D. The pathology and pathogenesis of retinal vasculitis. *Neuropathol. Appl. Neurobiol.* **29**, 325–340 (2003).[98]

did not (1.3 years versus 2.2 years; $P = 0.003$). In 3–7% of children with JIA, uveitis presents before arthritis;[8] for these patients, careful history taking and examination (together with ongoing follow-up) is needed to detect the underlying systemic disease.

Prognosis

JIA-associated uveitis is a sight-threatening disease, and several studies have described the frequency of ocular complications. A systematic literature review of outcomes in patients with JIA-associated uveitis showed an adverse visual outcome (visual acuity <20/40 in both eyes) in 9.2% of patients,[4] as well as cataracts (20.5%), glaucoma (18.9%) and band keratopathy (15.7%). Some evidence suggests that the frequency of complications might be decreasing with time.[14] In one study, which compared a cohort of 239 patients with JIA-associated uveitis from 1990–1993 to a similar cohort of 240 patients with JIA-associated uveitis from 2000–2003, complication rates were 35% and 21%, respectively. This apparent reduction could potentially be related to earlier use of systemic immunosuppressive agents, such as methotrexate, to treat joint disease (although evidence to confirm this suggestion is currently lacking). In another retrospective study of 35 patients (70 eyes) with JIA recruited during 1997–2005, 34% developed complications during follow-up (mean 5.62 years).[15] Although 91% of eyes had normal best corrected visual acuity, 5.6% were legally blind, and the remainder had some reduction in visual acuity.[15] The frequency of severe uveitis at diagnosis does not seem to have decreased over time, according to the results of a US study that compared two JIA cohorts with onset of joint symptoms before and after 1993, when JIA-associated uveitis screening guidelines were published.[16]

Several studies have looked at long-term follow-up data from patients with JIA-associated uveitis. Uveitis with onset in early childhood seems to have a biphasic course, with a reduction in anterior chamber activity at around age 9 years, after which it increases again in the early teenage years.[17] Another study described long-term complications in a cohort of 55 patients with JIA-associated uveitis treated at a single centre between 1973 and 1982.[18] At 7 years after uveitis onset, 42% had cataracts and 5% had glaucoma. At 24 years, 51% had cataracts, 22% had glaucoma and 49% had signs of active uveitis or were receiving topical corticosteroids to treat flares. A similar rate of persistence into adulthood of asymptomatic uveitis (almost 50%) was seen in a cohort of 19 patients with JIA-associated uveitis who were born in 1976–1980.[19]

Several factors are associated with a severe course of uveitis and the development of complications:[16,20,21] male sex; a young age at onset of uveitis; a short duration between onset of arthritis and development of uveitis; and the presence of synechiae at first diagnosis of uveitis. These adverse prognostic factors overlap to some extent with the risk factors for initial development of uveitis.

A retrospective case series of 65 children with JIA-associated uveitis showed significantly worse visual acuity in boys than in girls at 1 year and 3 years of follow-up.[22] The time interval between arthritis and uveitis onset is suggested to be the main predictor of uveitis severity, in that a short interval is associated with an increase in ocular complications.[23] Risk factors for visual loss, a key long-term outcome in patients with JIA-associated uveitis, were examined in a retrospective study of 327 patients (596 affected eyes).[24] The overall incidence of visual loss to 20/50 or worse was 0.18 cases per eye-year. The rate of developing a new ocular complication was 0.15 events per eye-year overall, but was substantially lower (0.04 events per eye-year) in those without such complications at baseline. The same study also showed that bilateral uveitis, a long duration of uveitis, presence of posterior synechiae, abnormal intraocular pressure (either <5 mmHg or >21 mmHg), active uveitis (grade ≥1+ anterior chamber cells or ≥0.5 vitreous haze) and a history of intraocular surgery were associated with worse vision during follow-up.

Presentation

Chronic anterior uveitis is usually asymptomatic, especially in its early stages. If symptoms occur they can include eye pain, redness, headache, photophobia and loss of vision, although these features tend to be more strongly associated with acute anterior uveitis than with chronic anterior uveitis, the form seen most frequently in JIA. JIA-associated uveitis often affects young children, who may be unable to reliably communicate changes in

Box 1 | Guidelines for uveitis screening in JIA*

Referral
Patients should be referred at the time of diagnosis or suspicion of JIA

Initial screening
First ophthalmological examination should be within 6 weeks of referral
Symptomatic patients or those suspected to have cataracts or synechiae should be seen within 1 week of referral

Ongoing screening
At 2, 4 and 6 months from onset of arthritis, then every 3–4 months, for a duration according to age at onset and category of JIA, as follows:

Oligoarticular, psoriatic and enthesitis-related arthritis, irrespective of ANA status, and age at onset <11 years:
- Age <3 years, duration of screening 8 years
- Age 3–4 years, duration of screening 6 years
- Age 5–8 years, duration of screening 3 years
- Age 9–10 years, duration of screening 1 year

Polyarticular arthritis, ANA-positive, and age at onset <10 years:
- Age <6 years, duration of screening 5 years
- Age 6–9 years, duration of screening 2 years

Polyarticular arthritis, ANA-negative, and age at onset <7 years:
- All children, duration of screening 5 years

Systemic JIA and rheumatoid-factor-positive, polyarticular JIA:
- Very low risk of uveitis; however, diagnosis can be uncertain at early stages and initial screening might, therefore, be indicated

All disease categories, onset >11 years:
- All children, duration of screening 1 year

Screening after stopping immunosuppression, such as methotrexate
At 2, 4 and 6 months after drug withdrawal, then revert to previous screening frequency as above

After discharge from screening
Advise about regular self-monitoring (by checking vision uniocularly once weekly) and when to present; an annual check by an optometrist is a useful adjunct

*Summarized from information published by the British Society for Paediatric and Adolescent Rheumatology and Royal College of Ophthalmology.[25] Abbreviations: ANA, antinuclear antibody; JIA, juvenile idiopathic arthritis.

their vision to their parents or carers. Therefore, regular screening of the eyes by an ophthalmologist or other appropriately trained health-care professional is vital for early detection and monitoring of the condition. Guidelines for such screening have been published in the UK (Box 1),[25] Germany[26] and the USA.[27] The British Society for Paediatric and Adolescent Rheumatology standards of care recommend that children should have their first ophthalmological assessment within 6 weeks of JIA being diagnosed or the diagnosis being suspected.[28]

Ophthalmological assessment

Routine ophthalmological assessment of children with uveitis involves age-appropriate tests of visual acuity, measurement of intraocular pressure, and slit-lamp assessments of the anterior and posterior chambers and retina. The SUN guidelines[2] for clinical trials of uveitis define standardized sets of criteria for grading intraocular inflammation, albeit principally for use in adults, in terms of anterior chamber cells, anterior chamber flare, vitreous cells, and vitreous haze or debris (Box 2). In particular, these guidelines highlight that grade 0.5+ anterior chamber cells should not be considered inactive uveitis.[2]

The breakdown of the blood–aqueous-humour barrier that occurs in uveitis is responsible for protein leakage into the anterior chamber, which can be measured as anterior chamber flare. The standard method of assessment is with a slit lamp.[29] However, an alternative and potentially more quantitative and reproducible method is laser flare photometry. A retrospective study showed that baseline laser flare ≥20 photon units per millisecond was associated with an increased risk of vision loss and ocular complications, including glaucoma.[30] This association seemed to be independent of the anterior chamber cell grade.[30] Similar findings were reported in another study, suggesting that routine measurements of laser flare in patients with JIA-associated uveitis might aid the identification of children at risk of complications and poor visual outcomes.[29]

Routine clinical examination of children with JIA-associated uveitis also requires assessment of the fundus and macula. Optical coherence tomography can be used to measure the thickness of the macula and fovea. Cystoid macular oedema is identified as increased thickness of the macula and loss of its normal concave shape. In a cross-sectional prospective study of macular lesions in 38 patients with JIA-associated uveitis (62 eyes), maculopathy was noted in 82% of eyes—only four eyes did not show any macular involvement.[31] The results of this study highlight that macular involvement might be much more frequent in patients with JIA-associated uveitis than has been suggested in other reports (which described this complication in up to 37% of eyes).[32] However, optical coherence tomography is required to detect subtle macular changes that are not identifiable on biomicroscopy.

The routine measurement of intraocular pressure is a particularly important part of uveitis screening, since intraocular hypertension and glaucoma can develop even after attaining control of active inflammation. A retrospective analysis of data on 30 patients (42 affected eyes) with JIA-associated uveitis showed that the first elevation in intraocular pressure occurred during a time of inactive disease in 60% of eyes, and that the mean time between achieving inactive disease status and first detection of elevated intraocular pressure was 4.5 ± 5.3 months.[33]

Consensus-based guidelines focusing specifically on outcome measures for use in prospective trials of JIA-associated uveitis have been developed.[34] In addition to uveitis activity, which is measured by anterior chamber cells, anterior chamber flare and the number of visits with active uveitis, these guidelines highlight visual acuity as a key outcome. Best corrected visual acuity should be measured using age-appropriate tests, recorded monocularly and binocularly, and the results should be converted to the logMAR (logarithm of the minimum angle of resolution) score. Comparisons based on data obtained at the most recent follow-up are flawed, since the test might have been performed at a variable time after the start of a particular therapy, which can introduce bias.[35] Instead, outcomes should be reported at fixed time points, such as 3 months, 6 months and 1 year after commencing therapy, if follow-up is almost complete. If the number of patients lost to follow-up is substantial, the rate of visual acuity loss per eye-year below a given threshold should be reported instead.

Visual acuity is a measure of both disease activity and damage, which results not only from long-term uncontrolled active uveitis but also from complications of treatment. Other structural features can also be signs of current and past disease activity, including synechiae, cataracts, macular oedema, band keratopathy, epiretinal membrane formation, ocular hypertension or glaucoma, ocular hypotony and vitreous haze. Although recording all these features at routine screening may not be possible or necessary, they are important clinical measurements and their use is recommended for all prospective trials in JIA-associated uveitis.

The adverse impact of eye disease on a young person's quality of life is well-known. However, an assessment tool to measure vision-related quality of life in children was developed only recently, in 2010. The Effects of Youngsters' Eyesight on Quality of Life (EYE-Q)[36] questionnaire was initially validated in a population of 120 children aged 8–18 years with JIA-associated uveitis, of whom 46.7% had no visual impairment and 52% had bilateral eye involvement.[37] At this stage, however, further validation and adaptation for different countries is required before this uveitis-related quality of life tool can be widely adopted.

Box 2 | Criteria for uveitis activity*

Grading schemes

Anterior chamber cells‡

- Grade 0 (<1) Inactive disease
- Grade 0.5+ (1–5)
- Grade 1+ (6–15)
- Grade 2+ (16–25)
- Grade 3+ (26–50)
- Grade 4+ (>50)

Anterior chamber flare

- Grade 0: None
- Grade 1+: Faint
- Grade 2+: Moderate (iris and lens details clear)
- Grade 3+: Marked (iris and lens details hazy)
- Grade 4+: Intense (fibrin or plastic aqueous)

Activity of uveitis terminology

- Worsening of activity: two-step increase in level of inflammation (for example, in anterior chamber cells or vitreous haze§ or increase from grade 3+ to grade 4+
- Improvement in activity: two-step decrease in level of inflammation (for example, in anterior chamber cells or vitreous haze) or decrease to grade 0
- Remission: inactive disease for ≥3 months after discontinuing all treatments for eye disease

*Published by the Standardisation of Uveitis Nomenclature (SUN) international working group. ‡Numbers in brackets represent the number of cells per field, when field size is a 1 mm by 1 mm slit beam. §A grading scheme for vitreous haze (not shown) is described elsewhere.[115] Permission obtained from Elsevier © Jabs *et al.* Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am. J. Ophthalmol.* **140**, 509–516 (2005).[2]

Pathogenesis

Although the strong association between JIA and uveitis has long been recognized, the cause of the intraocular inflammation is not fully understood.

Cellular immunology

Evidence of direct T-cell involvement in JIA-associated uveitis is lacking, even though noninfectious uveitis is recognized as a T-cell-mediated disease involving $CD4^+$ T cells of T helper type 1 (T_H1) and T_H17 subsets, which produce IFN-γ and IL-17 respectively (Figure 2).[38–40] These proinflammatory T cells are counterbalanced by $CD4^+$ $CD25^+$ $FoxP3^+$ T regulatory (T_{REG}) cells and inducible T_{REG} cells. Evidence for a role of T_H1, T_H17 and T_{REG} cells in noninfectious uveitis is derived from studies in both mice and humans, although the exact implications of each subset in the course of disease have not been refined.[1,41,42] Immunohistochemistry studies of biopsies from 12 eyes of patients with JIA-associated uveitis showed variable levels of $CD20^+$ cells and predominance of $CD4^+$ cells compared with $CD8^+$ cells; plasma cells and macrophages were the other cell types most consistently present.[1] A study of a single enucleated eye from a child with JIA-associated uveitis revealed focal aggregation of $CD20^+$ cells, with some $CD3^+$ and $CD8^+$ cells, as well as a few $CD4^+$ and $CD68^+$ cells.[43]

Lymphocytes and macrophages exert proinflammatory effects through secretion of cytokines and chemokines. Among 11 children with JIA-associated uveitis, levels of IL-2, IL-6, IL-13, IL-18, IFN-γ, TNF, soluble ICAM-1 (also known as CD54), C-C motif chemokine 5 (CCL5, also known as RANTES) and C-X-C motif chemokine 10 (CXCL10, also known as IP-10) in the aqueous humour were considerably higher than in controls without uveitis.[44] The recruitment and activation of mediators of innate immunity is required for full expression of the varied phenotypes of noninfectious uveitis in animal models. However, since autoimmunity and autoinflammation involve different molecular pathways, even though some convergence occurs, we need to increase our understanding of their respective roles in the development of noninfectious uveitis.[45]

We are increasingly able to extrapolate from human studies involving peripheral serum or cell analysis, and potentially early ocular biopsy sampling from the anterior chamber. However, the restricted availability of eye biopsy samples from patients with JIA-associated uveitis, and the fact that these patients are often receiving topical or systemic therapy, limits the knowledge gained. To elucidate further, we need to recruit large cohorts of patients for full immunophenotyping and genotyping.

Genetics

Although familial cases of JIA-associated uveitis have been reported,[46] concordance for uveitis among 49 sibling pairs with JIA was no higher than expected by chance, which argues against the presence of substantially increased sibling recurrence rates in JIA-associated uveitis.[47] Current evidence suggests that both JIA and uveitis are complex genetic traits, and monogenic or Mendelian patterns of inheritance have not been seen in families affected by JIA-associated uveitis.[48] Uveitis in patients with oligoarticular JIA has also been linked with the HLA-DR5 haplotype and HLA-DRB*1104 allele; the combination of HLA-DRB1*1104 and HLA-DPB1*0201

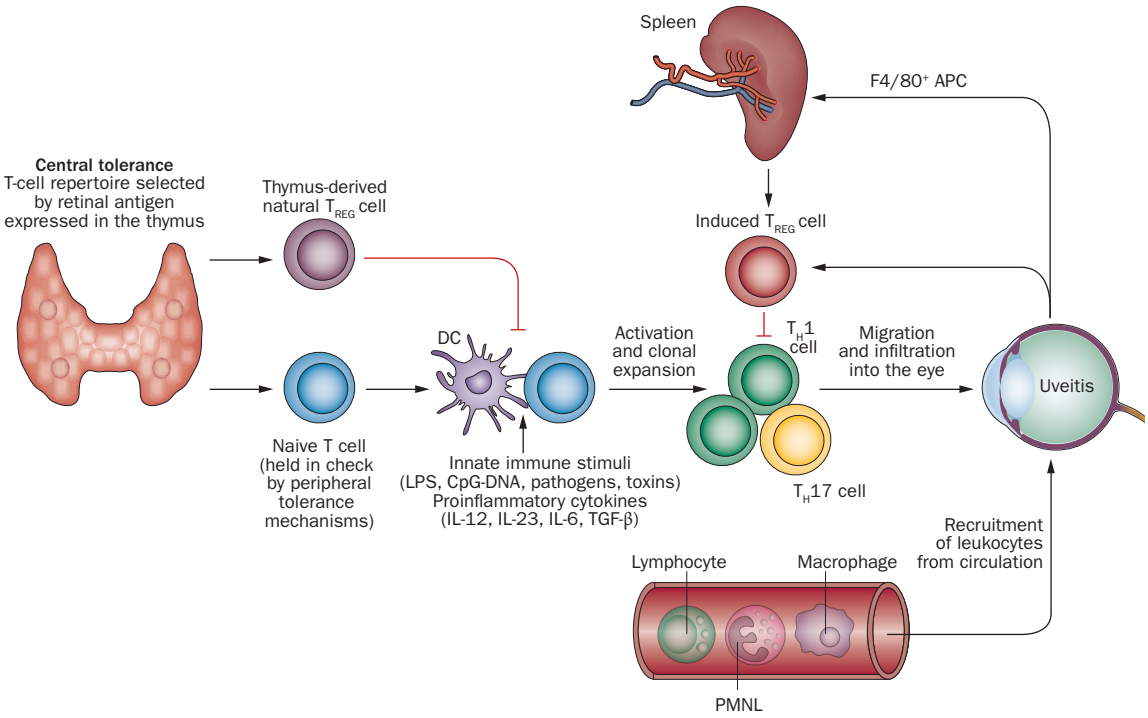

Figure 2 | Immunopathogenesis of uveitis. Incomplete thymic elimination of effector T cell precursors capable of recognizing retinal antigens, combined with deficient peripheral tolerance, results in persistence of circulating, non-tolerized T cells. These cells become activated by exposure to retina-derived or crossreactive antigens in conjunction with exogenous or endogenous inflammatory signals, and differentiate to an autoaggressive T_H1 or T_H17 phenotype. Although natural T_{REG} cells exported from the thymus inhibit activation and clonal expansion of these precursors, some activated effector T cells still reach the eye. Recognition of the cognate ocular antigen initiates a cascade of inflammatory events resulting in breakdown of the blood–retinal barrier, recruitment of leukocytes and uveitis. However, retina-derived antigens released from the damaged tissue can induce generation of antigen-specific T_{REG} cells via a spleen-dependent process, helping to terminate the inflammatory process and limit ocular pathology. Abbreviations: APC, antigen-presenting cell; DC, dendritic cell; LPS, lipopolysaccharide; PMNL, polymorphonuclear lymphocyte; T_H, T helper type; T_{REG}, T regulatory cell. Permission obtained from Wiley © Caspi, R. R. A look at autoimmunity and inflammation in the eye. *J. Clin. Invest.* **120**, 3073–3083 (2010) and Caspi, R. R. Ocular autoimmunity: the price of privilege? *Immunol. Rev.* **213**, 23–35 (2006).[99]

is associated with a 7.7-fold increase in the risk of chronic uveitis.[49,50] By contrast, the HLA-DR1 haplotype and HLA-DQA*0101 allele are protective. HLA-B27, which is associated with enthesitis-related arthritis, confers an increased risk of acute anterior uveitis.[51] These associations with HLA type support the current theory that JIA-associated uveitis is an autoimmune disorder, in which uveitis is thought to result from the loss of tolerance to several intraocular proteins, including S-arrestin (also known as retinal S-antigen), retinol-binding protein 3 (RBP3), and tyrosinase-related proteins.[52]

Limitations of animal models

Although several animal models[38,53] enable study of active uveitis at the tissue, cellular and protein level without the potential confounding effects of immunosuppressive treatment, no single model is ideal for investigating the immunopathogenesis of JIA-associated uveitis. Experimental autoimmune uveoretinitis in mice or rats can replicate many key features of the human disease in adults. However, this animal model and others do not parallel the clinical or pathological features of chronic anterior uveitis associated with arthritis observed in the few human studies available.

Animal models of intraocular inflammation, whether spontaneous or induced through standard immunization protocols (using retinal antigen and adjuvant) or specific T cell transfer, do not trigger a 'clinical' systemic disease—in particular, they do not induce arthritis.[54] Furthermore, the uveitis induced by endotoxin and melanin-associated antigen or collagen exposure is an acute or subacute and self-resolving condition that does not follow the course of the clinical disease we see in children.[55,56] For example, although compelling evidence supports the presence of a generalized proinflammatory state in human JIA-associated uveitis[44] and histological analysis indicates both T cell and B cell involvement in this disorder,[1] evidence of innate immune activation is lacking. In animal models, by contrast, a heightened innate response of monocyte and macrophage activation drives the observed tissue damage.[53]

Nonetheless, taking all evidence from the various models together (as when extrapolating from models of uveitis and spondyloarthropathy[57]), we can still use these models to unravel the underlying mechanisms and identify potential therapeutic targets for JIA-associated uveitis. The development of improved treatments also requires the effective translation of these new findings from bench to bedside.[53]

Autoantibodies

The question of whether systemic autoantibodies are involved in the pathogenesis of JIA-associated uveitis has been raised by the association of uveitis with ANA positivity.[58] However, other evidence of any associations between JIA-associated uveitis and groups of autoantibodies or autoantigens, or damage-associated and pathogen-associated molecular pattern molecules (DAMPs and PAMPs, respectively) is lacking. Whether these autoantibodies, DAMPs and PAMPs lead directly to autoimmunity or activation of innate immunity,[59] representing similar mechanisms to those observed in autoinflammatory diseases, is currently unclear. Although a positive correlation between ANA titres and plasma cell infiltration in patients with anterior uveitis has been reported, the intraocular antigens targeted by ANAs (and whether ANAs are actually pathogenic) are not clear.[1] In an attempt to detect autoantibodies against intraocular targets, researchers have incubated sera from patients with JIA and active uveitis with frozen sections of whole human eye tissue.[60] Using immunofluorescence, they demonstrated an increased frequency of antibodies against the iris and retina, but not the ciliary body, in sera from patients compared with sera from healthy control individuals. A similar study looked at antibody binding to sections of swine eyes after incubation with sera from children with JIA-associated uveitis, JIA without uveitis, idiopathic anterior uveitis or healthy controls.[61] In the patients with JIA-associated uveitis, antibody binding was predominantly to the iris (in 74%) and ciliary body (79%). Antibody binding showed a statistically significant correlation with the prevalence of ocular complications. However, owing to the fact that serum samples were obtained from these patients after the disease was already established, these observations cannot shed light on whether anti-ocular antibodies are part of the cause or consequence of uveitis. In the future, studies of samples taken at uveitis onset could enable the potential prognostic significance of antibody binding to be investigated.

Treatment

Currently, the treatment of all forms of JIA-associated uveitis follows a broadly similar stepwise therapeutic pathway.[62]

Topical steroids

The first-line treatment is topical corticosteroids.[62–64] High-potency steroids, such as prednisolone acetate 1% or dexamethasone phosphate 0.1%, have the greatest efficacy.[65] The frequency of administration of steroid eye drops is adjusted according to the degree of inflammation, usually ranging from once daily to hourly.

Interdisciplinary guidelines on management of JIA-associated uveitis recommend that topical steroid treatment is started when the anterior chamber cell grade is >0.5+.[62] Therapy is also advised when there is fibrin in the anterior chamber and keratocytic precipitates with corneal oedema and loss of visual acuity. The goal of treatment is a persistent anterior chamber cell grade 0. The absence of improvement in inflammation or presence of poor prognostic factors (poor initial vision, cataract, macular oedema, dense vitreous body opacification, ocular hypotony and glaucoma) are associated with loss of vision and necessitate increases in immunosuppressive treatment. Cataracts, glaucoma, synechiae and band keratopathy alone, in the absence of active uveitis, do not require anti-inflammatory treatment.[62]

Long-term, frequent treatment with steroid eye drops is clearly associated with an increased incidence of cataracts.[66] In an observational study, ≤3 drops daily of topical corticosteroids was associated with a significantly lower risk of cataracts than >3 drops daily (RR 0.13, 95% CI 0.02–0.69; $P = 0.02$).[66] We have therefore argued previously for the early introduction of steroid-sparing immunosuppression in patients with moderate to severe JIA-associated uveitis.[67]

Local and systemic steroids

Topical steroids alone can be effective, but severe or sight-threatening JIA-associated uveitis sometimes requires either local (periocular or intraocular) or systemic corticosteroids to achieve rapid control of inflammation. Systemic steroids can be given either orally (prednisolone 1–2 mg/kg daily) or as intravenous pulses (methylprednisolone 20–30 mg/kg daily for 1–3 days).[64] Although systemic steroids are highlighted as options in treatment guidelines,[62] published data supporting their efficacy in uveitis are limited to studies in adults.[68,69] Moreover, cumulative long-term use of systemic steroids is associated with well-known adverse effects, and these agents should be tapered to zero as early as possible.

Systemic DMARDs

Failure to achieve adequate control of inflammation after 3 months of topical treatment, particularly if >3 drops daily of topical corticosteroids are used, is an indication for systemic immunosuppression with a DMARD.[62]

Nonbiologic agents

A wide range of nonbiologic immunosuppressive agents are used to treat JIA-associated uveitis (Table 1). Controlled clinical trials of these drugs in management of JIA-associated uveitis have not been performed; therefore, the evidence base derives mainly from retrospective case series.

Methotrexate remains the preferred second-line therapy after topical corticosteroids. A systematic review and meta-analysis identified nine eligible studies of methotrexate use in noninfectious uveitis, including a total of 135 patients, of whom 121 had JIA.[70] The most commonly used dose was 15 mg/m^2, although doses of up to 30 mg/m^2 have been used, given as subcutaneous injections.[71] Overall, improvements in intraocular inflammation were seen in 73% (95% CI 67–81%) of patients with noninfectious uveitis. Among the 107 children for whom data were available, 19.6% experienced adverse events associated with methotrexate, most commonly gastrointestinal discomfort, nausea and elevated liver enzyme levels. Methotrexate treatment is associated with reduced need for cataract extraction; in a retrospective

Table 1 | Nonbiologic drugs used to treat JIA-associated uveitis

Drug name	Mechanism	Dosage and route	Common adverse effects	Evidence
Methotrexate	Cellular adenosine release[100]	10–15 mg/m^2 once weekly, oral or subcutaneous	Gastrointestinal discomfort, nausea, elevated liver enzyme levels	Systematic review and meta-analysis of retrospective case series (n=135): improvement in 73%[70]
Azathioprine	Purine nucleoside analogue, inhibits DNA replication	1 mg/kg once daily, increasing up to a maximum of 3 mg/kg once daily	Gastrointestinal discomfort, bone marrow suppression, liver function impairment	Retrospective case series (n=41): uveitis inactivity in 61.5% as initial monotherapy; 66.7% as combination therapy[101]
Mycophenolate mofetil	Inhibitor of inosine-5-monophosphate dehydrogenase	300 mg/m^2 twice daily, increasing to 600 mg/m^2 twice daily	Gastrointestinal discomfort, leukopenia, hair loss	Retrospective case series (n=17, n=52, n=85, not all with JIA; various outcome measures): response in 55–88%[102–104]
Ciclosporin	Calcineurin inhibitor; blocks T-cell proliferation	2.5–5.0 mg/kg daily in 2 doses	Gastrointestinal disturbance, hypertension, renal and liver dysfunction, lipid abnormalities	Retrospective case series (n=82, n=14): uveitis inactivity in 24% as monotherapy, 48.6% as combination therapy[105,106]
Tacrolimus	Calcineurin inhibitor; blocks T-cell proliferation	50–150 μg/kg twice daily	Gastrointestinal disturbance, hypertension, renal and liver dysfunction, lipid abnormalities, blood disorders	Retrospective case series (n=62, mostly adults with idiopathic uveitis): enabled glucocorticoid tapering and improved visual acuity[107]

study, 29% of methotrexate-treated patients with JIA-associated uveitis required cataract surgery, compared with 64% of those who never received this agent.[72]

One study has examined relapse after withdrawal of methotrexate. In a retrospective case series of 22 patients with JIA-associated uveitis who were treated with methotrexate, the drug was discontinued in 13 patents who achieved inactive disease status, which occurred after a mean of 1.5 years of inactive disease and a mean duration of therapy of 3.1 years.[73] Relapse-free survival was significantly longer in patients treated for >3 years, children aged >8 years when methotrexate was withdrawn, and those who had inactivity of uveitis for >2 years before withdrawal. Sustained disease inactivity while receiving methotrexate was associated with a substantial decrease in the risk of relapse after drug withdrawal (HR 0.07, 95% CI 0.01–0.86; P = 0.038), implying that a 1 year increase in the duration of inactive uveitis before withdrawal of methotrexate would decrease the risk of relapse by 93%. Other nonbiologic DMARDs used less frequently than methotrexate in the treatment of JIA-associated uveitis include azathioprine, mycophenolate mofetil, ciclosporin and tacrolimus (Table 1).[64,74]

Biologic agents

The past decade has seen a shift in the management of JIA-associated uveitis with the arrival of biologic agents (Table 2).[75] The strongest evidence so far supports the use of adalimumab in treatment of JIA-associated uveitis. A double-blind, randomized controlled trial of etanercept in 12 patients with JIA-associated uveitis showed no difference between the drug and placebo,[76] and numerous studies have reported new-onset uveitis or flares of uveitis in patients receiving etanercept.[77–79] Although clear evidence is lacking that etanercept actually causes uveitis, and this symptom can also occur in patients receiving adalimumab or infliximab, data from national registries show that etanercept treatment is associated with a greater incidence of uveitis than is seen with either adalimumab or infliximab therapy.[80] Therefore, etanercept is not recommended in patients with JIA-associated uveitis. The results of a 2014 meta-analysis including 229 children with JIA-associated uveitis showed that infliximab has similar efficacy to adalimumab, and that both are superior to etanercept.[81] However, during 40 months of follow-up, uveitis more commonly remained in remission in those treated with adalimumab rather than infliximab: nine of 15 adalimumab-treated patients remained in remission (60%), versus three of 16 infliximab-treated patients (18.8%).[82] In a small case series, switching between anti-TNF agents, particularly switching to adalimumab after loss of efficacy of infliximab, enabled control of uveitis to be regained.[83] No studies have systematically investigated treatment options after failure of an anti-TNF agent, although other biologic therapies—notably tocilizumab, abatacept and rituximab—are sometimes used to treat JIA-associated uveitis (Table 2). Efficacy of these other agents has been shown in most studies, although only small numbers of patients have been included.

Evidence of the efficacy and safety of biologic treatments specifically in a JIA-associated uveitis population is still needed. The SYCAMORE study, a randomized, placebo-controlled multicentre trial of adalimumab for JIA-associated uveitis, is currently recruiting patients.[84] Another randomized controlled trial of adalimumab conducted in France is awaiting publication.[85] Smaller studies are also underway or planned to examine tocilizumab and abatacept in JIA-associated uveitis.[86,87]

Surgery

Some complications of uveitis, including cataracts and glaucoma, might require surgical treatment. If a cataract substantially impairs visual acuity, the standard surgical

Table 2 | Biologic agents used to treat JIA-associated uveitis

Drug name	Target	Drug class	Dosage and route	Evidence
Etanercept	TNF	Dimeric fusion protein	Not recommended for treatment of JIA-associated uveitis	RCT: no more effective than placebo Case reports of new uveitis on etanercept[76,81]
Infliximab	TNF	Chimeric (mouse–human) mAb	6 mg/kg intravenous initially, then 3–10 mg/kg Second dose at 2 weeks, then every 4–8 weeks depending on response	Several case series showing efficacy[81]
Adalimumab	TNF	Fully human mAb	24 mg/m^2 subcutaneously every 2 weeks In practice often 20 mg subcutaneously every 2 weeks (body weight <30 kg) or 40 mg subcutaneously every 2 weeks (body weight ≥30 kg)	Several case series showing efficacy RCTs in progress[81,84]
Golimumab	TNF	Fully human mAb	50 mg subcutaneously every 4 weeks	Case series (n=3) showing efficacy[108]
Tocilizumab	IL-6	Humanized mAb	10 mg/kg (body weight <30 kg), 8 mg/kg (body weight >30 kg) intravenously every 4 weeks	Case series (n=3) and case report showing efficacy[86,109,110]
Abatacept	CD80/CD86 (CTLA4)	Fully human fusion protein	10 mg/kg intravenously at weeks 0, 2 and 4, then every 4 weeks	Case series (n=7, n=2) showing efficacy[87,111,112]
Rituximab	CD20	Chimeric (mouse-human) mAb	375 mg/m^2 or 750 mg/m^2 intravenously, in two doses 2 weeks apart	Case series (n=10, n=8) showing efficacy in most patients[113,114]

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; mAb, monoclonal antibody; RCT, randomized controlled trial.

treatment is removal of the lens by phacoemulsification.[88] Improved outcomes are associated with the control of intraocular inflammation in these patients, both perioperatively and postoperatively,[89,90] to achieve 'minimal' uveitis activity (an arbitrary yet accepted target) for at least 3 months before surgery. Glaucoma in the context of JIA-associated uveitis might also require surgical treatment. Elevations in intraocular pressure that are unresponsive to medical treatment can be managed surgically by goniotomy, insertion of a glaucoma drainage device or trabeculectomy.[91–93]

Biomarkers and outcome prediction

Further advances in the management of JIA-associated uveitis will require the development of validated biomarkers—none of the potential biomarkers described here has yet been validated. In particular, biomarkers are required to predict which children with JIA will develop uveitis and to detect preclinical flare of uveitis (thereby enabling rapid initiation of therapy and avoiding disease-related damage). In addition, biomarkers to predict which children with JIA-associated uveitis will respond best to a particular therapy would enable risk stratification and personalized medicine, whereas biomarkers to confirm the presence of disease remission by serological or other means would increase the success of withdrawal of therapy.

Despite the association of ANAs with uveitis, it is clear that ANA positivity alone cannot predict which children with JIU will develop uveitis. In one study, detection of ANAs by ELISA was not associated with uveitis, which suggests that this test should not be used to determine the frequency of eye examinations.[94] ANA assays based on indirect immunofluorescence might offer improved prediction of uveitis, however, particularly when high titres are found. In a cohort of 100 children with JIA, 16 developed uveitis, of whom 14 were positive for ANAs (titre ≥1:80 on immunofluorescence assay) and 13 were positive for antihistone antibodies (titre ≥ 8 U/ml). The authors of this study suggested that the combination of antihistone antibodies ≥ 8 U/ml, immunofluorescence-detected ANAs ≥1:320 and a young age at onset of JIA might identify a subgroup of patients at increased risk of developing chronic uveitis.[94]

A further predictor of an increased risk of uveitis seems to be an elevated erythrocyte sedimentation rate (ESR) at the time of diagnosis with JIA. In a retrospective chart review of patients with oligoarticular JIA who were recruited at the time of diagnosis,[95] data on demographics were collected, inflammatory markers were measured, and genotyping for allelic variants in genes encoding TNF, IL-1β, IL-6, IL-10 and IL-1Ra was performed. ESR was significantly higher in the group who developed uveitis versus those who did not (52 mm/h versus 24 mm/h, respectively; OR 1.05, 95% CI 1.01–1.09). ANA status and cytokine gene polymorphisms were not associated with development of uveitis. Multivariate analysis showed that ESR >22 mm/h and patient age <3 years at onset of arthritis were associated with ORs of 5.28 and 3.80, respectively, for the development of uveitis. The researchers suggest that treatment and disease outcomes might be improved by using these parameters to select a population for more intensive screening, or to predict which children will develop uveitis.

A potential intraocular biomarker for JIA-associated uveitis has been identified.[96] Researchers obtained aqueous humour samples from 17 patients with JIA-associated uveitis, 39 with other forms of uveitis and 20

control individuals without inflammatory disease.[96] In the JIA group, a protein later identified as transthyretin was expressed at a significantly higher level than in individuals with other forms of uveitis and controls. The exact role of transthyretin in JIA-associated uveitis, and whether it is involved in the pathogenesis of this disorder, is unclear.

One group has published preliminary data suggesting that mass spectrometry can identify a molecular signature associated with JIA-associated uveitis in tear samples.[97] The inherent risks associated with sampling the aqueous humour, and the easy accessibility of tear samples means that biomarkers in tears offer an increased likelihood of translation to clinical practice. These studies highlight a possible opportunity for proteomic studies to aid in understanding the biology of uveitis. Moreover, approaches including immunophenotyping, genetic studies and other potential platforms, including metabolomics, might in future deliver a composite risk or outcome identifier for JIA-associated uveitis.

Conclusions

JIA-associated uveitis remains a challenge for paediatric rheumatologists and ophthalmologists, as substantial numbers of children still develop sight-threatening complications. The main aims in management of JIA-associated uveitis are, therefore, early detection of disease and prompt initiation of treatment. Evidence-based guidelines have highlighted the importance of systemic immunosuppression with steroid-sparing agents in patients with persistently active uveitis. The ongoing development of biologic agents offers the prospect of more specific and potentially more efficacious therapies, increasing the available treatment options for JIA-associated uveitis. Prospective controlled trials of adalimumab are in progress, and other biologic agents are available to treat patients with steroid-refractory disease.

Although *in vitro* and animal studies of uveitis are identifying immune mechanisms linked to its pathogenesis, investigations specifically focusing on JIA-associated uveitis are currently sparse. In-depth understanding of the pathogenesis of JIA-associated uveitis could also help to identify novel biomarkers, either genetic or perhaps circulating factors, which would enable risk stratification and targeting of patients in high-risk groups for earlier and more aggressive therapy. The identification of predictive biomarkers to guide the use of the expanding therapeutic armamentarium will be another key goal for the coming years.

Review criteria

PubMed was searched for English-language published articles using the terms "juvenile idiopathic arthritis" OR "juvenile chronic arthritis" OR "juvenile rheumatoid arthritis" and "uveitis", in combination with "epidemiology", "diagnosis", "screening", "prognosis", "pathogenesis", "pathophysiology" "immunology", "treatment" and "therapy". The reference lists of selected papers were also searched for further relevant articles. The ClinicalTrials.gov registry was searched using the terms "uveitis" and "juvenile idiopathic arthritis" for trials which are currently recruiting.

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