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Managing Juvenile Idiopathic Arthritis-associated Uveitis

Hawkins, MJ [1]; Dick, AD [1, 2, 3] ; Lee, RJW [1, 2, 3]; Ramanan, AV [2,4]; Carreño, E [1]; Guly, CM[1]; Ross AH [1]

[1] Retinal Treatment and Research Unit, Bristol Eye Hospital, Bristol, UK.

[2] School of Clinical Sciences, University of Bristol, Bristol, UK.

[3] National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK.

[4] Department of Pediatric Rheumatology, Bristol Royal Hospital for Children, Bristol, UK.

***Corresponding author:**

Adam H. Ross

Bristol Eye Hospital

Medical Retina and Uveitis department

Lower Maudlin St,

Bristol BS1 2LX

Email: Adam.Ross@bristol.ac.uk

Abstract. Bilateral chronic anterior uveitis is an extra-articular feature of Juvenile Idiopathic Arthritis (JIA). Although figures vary, uveitis occurs in approximately 11-13% of patients with this disease, and is most commonly associated with the female gender, oligoarthritis and presence of antinuclear antibodies. The disease has an insidious onset and is often asymptomatic. Managing patients with JIA-associated uveitis remains challenging as the disease may prove to be refractory to traditional treatment regimens. Stepwise immunomodulatory therapy is indicated for the treatment of JIA-associated uveitis, with new biological drugs being utilized last in cases of refractory uveitis. Small scale studies and practice have provided the evidence to undertake randomized control trials to evaluate the efficacy, safety and cost-effectiveness of anti-TNF-α therapies, such as Infliximab and Adalimumab. These have demonstrated promising results, with further data awaited from ongoing trials for Adalimumab (as SYCAMORE and ADJUVITE trials). Lower grade evidence is supporting the use of newer biologics such as Rituximab, Daclizumab, Tocilizumab and Abatacept, in those cases refractory to anti-TNF-α therapy.

I. Introduction

Juvenile Idiopathic Arthritis (JIA) is a heterogeneous group of arthritides presenting in childhood. To meet the criteria for diagnosis set out by the International League of Associations for Rheumatology (ILAR), the child (under 16 years of age) must have unexplained arthralgia for a duration of 6 or more weeks.[1] It is the most common arthritis to present in the pediatric population.[2] Whilst joint pain and immobility are the most pertinent features, the most common extra-articular feature of JIA is uveitis, particularly anterior uveitis. In some patients, uveitis proves to be refractory to standard therapeutic measures, presenting a management challenge to ophthalmologists. This paper seeks to stress the importance of prompt recognition and management of JIA-associated uveitis and explores current research on the efficacy of biological agents for its treatment. Based on a systematic review of the literature and our clinical experience, a guide used at the Bristol Eye Hospital, UK is provided for the escalating treatment of these complex patients.

II. Definition and Epidemiology of Juvenile Idiopathic Arthritis

JIA is an autoimmune condition in which dysregulation of pro-inflammatory cytokines results in activation of T-cells in the synovial tissue.[3; 4] Data on incidence and prevalence vary and is possibly unreliable due to the heterogeneous nature of the disease and different classification criteria available. Prevalence is estimated to be between 0.07 - 4.01 per 1000 and the incidence between 0.008 - 0.226 per 1000.[2] Studies mainly focus on Caucasian populations so little is known about the

epidemiology of other races. From European studies, it appears that the most common subtype is oligoarthritis (50-70%), followed by rheumatoid factor-negative polyarthritis (30%).[5]

III. Genetics of Juvenile Idiopathic Arthritis

Involvement of genetic factors in the etiology JIA has been strongly suggested by twin concordance studies. At 25-40%, twin concordance is much higher than the population prevalence.[6] Although reports of multicase families are rare, one Finnish study indicated that siblings of patients appear to be at greater risk of developing JIA. Further research demonstrated this risk to be 15-30 times greater than the general population.[7; 8; 9]

Data indicates specific polymorphisms in Human Leukocyte Antigen (HLA), Macrophage Inhibitory Factor (MIF) and Protein Tyrosine Phosphatase (PTPN22) genes could increase susceptibility to JIA, but these will only explain a portion of the overall genetic background of JIA as it is a complex genetic trait.

A strong risk association has been found between certain forms of JIA and HLA alleles. The association appears strongest in oligoarthritis, particularly with HLA Class II alleles. The association with HLA-DR has been shown in polyarticular arthritis,[10] whilst HLA-B27 is associated with enthesitis-related arthritis.

Conversely, some HLA alleles (B27 and DR4) have a protective influence in early age, yet pose a risk later on.[11]. Some HLA allele profiling studies show that the presence of the HLA allele DRB1*1104 significantly increases the risk of developing uveitis in oligoarticular JIA,[12; 13] but other larger studies are not so conclusive.[14] Studies have used JIA sibling pairs to determine the developmental role of genetics

for uveitis, but little conclusive evidence has been found for a specific genetic element.[15; 16; 17]

Research has also implicated the MIF and PTPN22 genes.

MIF has a role in production of inflammatory cytokines such as IL-1, IL-6, and IL-8, and also promotes macrophage intracellular killing and phagocytosis. A review of current evidence into genetic susceptibility for JIA by Phelan et al. implicated a functional role for MIF in the pathogenesis of JIA, particularly the -173*C allele in systemic disease.[18]

PTPN22 is an intracellular tyrosine phosphatase in T-cells, which lowers the threshold for T-cell receptor signaling. A single-nucleotide polymorphism (1858C/T; rs2476601) has been associated with JIA, as has the 1858*T allele.[18; 19]

A dense genotyping study including 2,816 patients with JIA and 13,056 controls confirmed the previously known association of the HLA region, and PTPN2, and also identified 14 other loci associated with JIA, including genes involved in the IL-2 pathway.[20]

IV. Classification

Nomenclature for childhood arthritis has varied over the years. Since the ILAR published their new criteria in 2001, Juvenile Idiopathic Arthritis is the most widely used and accepted term, making older terms such as Still's disease, juvenile chronic arthritis and juvenile rheumatoid arthritis obsolete. ILAR set out seven subtypes encompassed under the term JIA, which vary in terms of presentation, clinical signs, severity and family history,[21] namely: systemic arthritis, oligoarthritis ('persistent' and 'extended'), rheumatoid factor-positive or negative polyarthritis, enthesitis-related

arthritis, psoriatic arthritis and undifferentiated arthritis. The epidemiology of these is listed in Table 1.

A. Systemic Arthritis

Systemic arthritis is the most severe form of JIA, and frequently begins with a characteristic spiking fever. This can be coupled with a rash, myalgia, lymphadenopathy and hepatosplenomegaly, but polyarthritis may not present for weeks to months after the initial presentation. Uveitis is extremely rare in this subtype.

B. Oligoarthritis/Pauciarthritis

Oligoarthritis is the most common subtype, occurring more frequently in girls than boys. In the 'persistent' form, up to 4 joints are affected. If after 6 months, the number of affected joints increases to more than 4, this is termed the 'extended' form.

C. Rheumatoid factor-positive polyarthritis

Rheumatoid factor-positive polyarthritis affects 5 or more joints in a rheumatoid factor (RF)-positive child. It tends to affect older children and teenagers.

D. Rheumatoid factor-negative polyarthritis

Rheumatoid factor-negative polyarthritis affects 5 or more joints. It presents at all ages peaking in a biphasic pattern at 2-4 years and 9-11 years. It is more common than rheumatoid factor-positive polyarthritis.

E. Enthesitis-related arthritis

Any number of joints may be affected in enthesitis-related arthritis along with inflammation of tendons or muscular attachment to bone. It is most common in boys, and in addition to the above criteria, two or more of the following must also be present: HLA-B27 antigen positive, HLA-B27 associated disease in first-degree relative, sacroiliac joint tenderness, acute anterior uveitis or inflammatory lumbosacral pain.

F. Psoriatic Arthritis

Psoriatic arthritis is RF-negative coupled with signs and symptoms of psoriasis such nail changes, dactylitis, psoriatic plaques or a family history. It is usually an asymmetric oligoarthritis.

G. Undifferentiated Arthritis

Patients who do not fulfill the criteria for any subtype, or patients who fulfill the criteria for more than one subtype have Undifferentiated Arthritis.[1; 22; 23; 24]

V. Epidemiology of Juvenile Idiopathic Arthritis associated Uveitis

Uveitis, inflammation of the uveal tract, is strongly associated with JIA. All anatomical types of uveitis are associated with JIA, but anterior uveitis is by far the most common (83%). Less frequently occurring are intermediate uveitis (9%), posterior uveitis (1%) and pan-uveitis (7%).[25] Both girls and boys can be affected, although evidence suggests girls under the age of 7 at diagnosis of JIA have a greater risk of developing uveitis, as do anti-nuclear antibody (ANA) positive children [26]. A recent study found that an elevated erythrocyte sedimentation rate appeared to be a

predictive factor for development of uveitis, together with young age at onset and presence of ANA.[27] The precise prevalence of uveitis amongst children with JIA is uncertain as figures vary in current literature. Figures between 8% and 45% have been quoted.[25; 28; 29; 30; 31]

The largest review by Heiligenhaus in 2007 quotes a JIA-associated uveitis prevalence of 12%. The study was population based with a cohort of 3271. Of the 12% with uveitis, 83% were ANA positive, 25% had extended oligoarthritis and 16% had persistent oligoarthritis. Furthermore, those with JIA and uveitis had an earlier onset of arthritis compared to those with arthritis alone; mean age 3.8 versus 7.0 respectively. Anterior uveitis was the most common in the group at 83%.[25]

A prospective observational case series by Kotaniemi et al detected uveitis in 24% of the 426-strong cohort. A high proportion of these were ANA positive (66%), and similarly oligoarticular arthritis was the most affected group at 27%. Children with JIA and uveitis had an earlier mean age of diagnosis of arthritis compared to children with arthritis alone (4.8 versus 7.3yrs).[29]

A Greek retrospective review studied the prevalence of JIA-associated uveitis. Of the cohort of 56, 45% had anterior uveitis. 28% of these had further ocular complications: cataracts (n=6), band keratopathy (n=4), posterior synechiae (n=3), glaucoma (n=1), phthisis bulbi (n=1) and hyphema (n=1). The mean age of developing uveitis was 56 months.[30]

Saurenmann et al also reported young age at diagnosis, female sex, and presence of antinuclear antibodies as strong risk factors for development of uveitis. Oligoarthritis was reported as the subtype with the highest rate of uveitis, and rheumatoid factor positive-polyarthritis as the subtype with the lowest rate; although the relative contribution of these risk factors was different for the different subtypes of JIA.[32]

VI. Etiology/pathogenesis of JIA-associated Uveitis

The pathogenesis of the JIA is very complex as it is clearly a heterogeneous and multi-factorial disease, with a likely distinct pathogenesis for the different types of JIA. Current research establishes a very different pathogenesis for oligoarthritis in contrast to systemic arthritis. Oligoarthritis is likely an autoimmune disease, caused by an abnormality of the adaptive immune system mediated by an antigen-driven lymphocyte-response, with a subsequent imbalance between autoreactive Th1/Th17 and regulatory T (Treg) cells, which leads to the loss of immune tolerance to self-antigens. However, systemic arthritis is considered an autoinflammatory disease (in contrast to autoimmune) with abnormality in the innate immune system leading to aberrant activation of phagocytes (monocytes, macrophages and neutrophils) with the increase of pro-inflammatory cytokines and chemokines (IL-1, IL-6, IL-18 and pro-inflammatory S100-proteins).[33]

The pathogenesis of JIA-associated uveitis is also complex and multi-factorial. Tissue studies have been performed, but these are usually carried out after years of chronic disease and so do not necessarily help to elicit the etiology of early phase disease.[31] Parikh et al carried out an immunohistochemical study of the iris and ciliary body of one eye with JIA-associated anterior uveitis. This demonstrated non-granulomatous inflammation consisting predominantly of B cells and plasma cells with focal collections of CD20+ cells. T cells were also present, but in fewer numbers, potentially due to previous use of an anti-TNF-α agent.[34] However, these non-specific changes do not particularly help to determine the pathogenesis.

Given that ANA-positive JIA patients clearly have an increased risk for uveitis,[35] ANA could have a role in the pathogenesis of uveitis. The reason for the association is not known, and no common nuclear antigen has been discovered.[36]

Other antibodies against retinal S-antigen and the DEK oncoprotein have also been implicated but evidence is conflicting. Edleston et al found no evidence for abnormal levels of antibodies to human or bovine retinal S-antigen in children with JIA-associated uveitis.[37] However, Petty et al found that an antibody to S-antigen in serum was present significantly more frequently in children with JIA-associated uveitis than in children with JIA alone, other rheumatology disorders or healthy controls, and the cellular response in peripheral blood lymphocytes, measured by lymphocyte transformation, was also more frequent in those patients with JIA-associated uveitis.[38] Murray et al found serum antibodies to the DEK protein to be characteristic of oligoarticular JIA,[39] however Dong et al found anti-DEK autoantibodies related to autoimmune conditions in general rather than specifically to JIA.[40] Walscheid et al described how antiocular serum antibodies to ocular cryosections from swine eyes were detected more frequently in JIA-associated uveitis than in control groups, correlating with a complicated uveitis course but not with uveitis activity or anti-inflammatory treatment.[41] Similarly, it has been also reported higher levels of transthyretin are present in the aqueous of patients with JIA-associated uveitis and silent chronic anterior uveitis compared to those of the other uveitis types and control groups.[42]

Recently, a study has shown an association between parvovirus B19 and JIA-associated uveitis. In this study an intraocular antibody production against parvovirus B19 was found by Goldmann-Witmer coefficient in 7 of 13 patients with JIA-

associated uveitis and only 3 of 45 patients with anterior uveitis of undetermined origin. However the viral DNA was not detected by PCR in any of the cases.[43]

Despite HLA associations, to date no clear auto-antigens or indeed autoantibody has been identified to implicate autoimmunity.

VII. Clinical Picture of Juvenile Idiopathic Arthritis-associated Uveitis

JIA-associated uveitis most frequently presents as a chronic anterior uveitis. Arthritis usually precedes the development of uveitis, but in approximately 10% of cases, uveitis presents before arthritis.[44; 45] When this is the case, treatment for the uveitis can delay the presentation of joint involvement. A recent study suggests JIA-associated uveitis has a biphasic course, with a second peak of activity in the early teens.[46] There is little solid evidence regarding activity of JIA-associated uveitis in adulthood as follow-up studies are often discontinued once the patient is over 16 years of age. JIA-associated uveitis can result in ocular complications such as cataracts, secondary glaucoma, synechiae, and band keratopathy.[25]

VIII. Screening

Due to the asymptomatic nature of JIA-associated uveitis, screening by slit lamp for uveitis is vital in children suffering from JIA.[47] In the United Kingdom, The British Society for Pediatric and Adolescent Rheumatology (BSPAR) and the Royal College of Ophthalmologists (RCOphth) have produced joint screening guidelines for uveitis in JIA (accessed at https://www.bspar.org.uk/DocStore/FileLibrary/PDFs/BSPAR%20Guidelines%20for

%20Eye%20Screening%202006.pdf), a modification of which is presented in Table 2. Specific screening schedules are suggested for different subtypes, taking into account the subtypes most at risk of developing uveitis.

IX. Management

A. Initial Management

1. Corticosteroids

Topical corticosteroid drops, such as prednisolone and dexamethasone, are the first line of treatment for JIA-associated uveitis. Studies have proved these to be more effective than placebo, however over time there are significant side effects, in particular raised intraocular pressure (IOP) and cataract formation.[48] Overall the cumulative topical corticosteroid dose correlates with significant visual impairment.[49] Elevated intraocular pressure secondary to steroid use is known as a steroid response, and persistent or recurrent episodes of elevated IOP may result in secondary glaucoma. Armaly et al used 85 healthy subjects to sub-categorize this steroid response into three groups: high, moderate and non-responders. One third of the study population had an increased IOP after daily topical corticosteroid use for 4 to 6 weeks, five percent of which were considered 'high responders' with elevations of IOP greater than 15 mmHg and a total IOP greater than 31 mmHg. Patients with rheumatoid arthritis were found to have higher rates of steroid responsiveness.[50]

Thorne et al. found that the incidence of new-onset cataract was increased in patients with JIA-associated uveitis taking topical corticosteroids (0.04/eye-year; 95% confidence interval 0.02-0.09).[49]

In complex disease, more aggressive therapy may be required; high dose systemic steroids including pulsed intravenous methylprednisolone may be useful (at a dose up to 30 mg/kg to max of 1 g). Prolonged use of systemic steroids should be avoided in children where possible due the associated side effects, including growth retardation.

2. Methotrexate

Other agents may be considered if an adequate response to topical steroids is not achieved in children with severe disease. According to the German guidelines for anti-inflammatory treatment of JIA-associated uveitis, Methotrexate should be considered when the intraocular inflammation has not responded to 12 weeks of topical corticosteroid treatment (maximally 3 times daily), or in those cases of recurring uveitis under a systemic corticosteroid dosage of more than 0.15 mg/kg body weight, or if there is a new development of uveitis complications.[51]

The antimetabolite Methotrexate is a common and effective choice for treating both joint inflammation and ocular inflammation. Although evidence for the use of Methotrexate in joint inflammation is strong, evidence specific to JIA-associated uveitis from randomized control trials and prospective studies is lacking. Ayuso et al. conducted a retrospective analysis of 22 patients, 18 of which (82%) showed improvement of their uveitis with a significant decrease in activity of inflammation after 3 months of Methotrexate treatment.[52] Relapse rates were high (69%), although remission after withdrawal of Methotrexate was significantly longer in those treated

for greater than 3 years (P = 0.009). Heilingenhaus et al. reported the outcome of treatment with Methotrexate in 35 patients with JIA-associated uveitis, achieving control of the inflammation without topical steroids in 21 patients and with topical steroids in 7 cases.[53] Another study looking at new uveitis onset among patients with JIA, showed a lower incidence of uveitis onset in the group treated with Methotrexate versus the group not treated with Methotrexate.[54]

The mean time to pharmacology induced remission after starting Methotrexate in JIA associated uveitis has been reported to be around 4.25 months, with a mean duration of the remission in those who achieved remission of 10.3 months.[55]

The side effect profile of Methotrexate includes gastrointestinal upset, peptic ulcers, stomatitis, mouth ulcers, rashes and infections.[56] Patients on Methotrexate require regular blood monitoring. Full blood count (FBC) and liver function (LFT) monitoring is required fortnightly until a stable dose is achieved. Subsequently, monitoring of FBC and LFTs should be monthly for six months, and six-weekly thereafter. Urea and electrolytes and creatinine are monitored six monthly.

Methotrexate can be administered orally, intramuscularly or subcutaneously. Folic acid supplements must be taken alongside the use of Methotrexate.[31]

The recommended standard dose for the treatment of JIA with Methotrexate is 10-15 mg/m^2/week based on a 1992 randomized double-blind placebo-controlled trial in patients with resistant arthritis.[57] Recent studies showed that the high-dose of Methotrexate is associated with greater risk of associated side effects, but no significant improvement in active joint count, so according to these results doses greater than 0.5 mg/Kg/week should be avoided.[58]

3. Mycophenolate mofetil

Mycophenolate mofetil (CellCept) is used to prevent rejection in transplants and stops the proliferation of lymphocytes. It has also been shown to be a useful adjunct in those with refractory uveitis with no joint involvement, resulting in improvement in uveitis and sparing the use of corticosteroids.[59] Some reports in adults, including patients with JIA-associated uveitis, have demonstrated Mycophenolate mofetil may be effective in maintaining vision and improving visual acuity.[60]

In the pediatric population, Mycophenolate mofetil has also shown efficacy on the treatment of pediatric uveitis. In a study by Doycheva et al. including 17 children with uveitis (4 with JIA-associated uveitis), Mycophenolate mofetil achieved a steroid-sparing effect in 88% of the patients, with complete discontinuation of oral prednisolone in 41%. 24% of the patients remained relapse-free during the treatment, and a reduction in the relapse rate was observed in all other patients except one.[59] In another study by Chang et al including 52 patients with pediatric uveitis (25 with JIA-associated uveitis), 73.1% achieved inflammation control after 2 months of treatment with Mycophenolate mofetil monotherapy. However, the treatment had to be stopped due to side effects in 6 patients (11.5%), specially gastrointestinal disturbances.[61]

No randomized controlled trials have been performed in this area. It should be noted that Mycophenolate mofetil is not routinely used in patients with severe joint disease because it is not considered to be effective in treating arthritis. A randomized controlled trial found no difference between placebo and Mycophenolate mofetil in terms of disease improvement in patients with refractory rheumatoid arthritis.[62]

The recommended dose for the use of Mycophenolate mofetil in JIA-associated uveitis is 1000-1500 mg/m^2 divided in two doses.[59]

4. Cyclosporin

A multicentre retrospective study of 82 patients looked into the effects of oral cyclosporin on the treatment of active uveitis in patients with JIA already taking topical or systemic steroids or other immunomodulatory agents. Inactive uveitis during the treatment period was only achieved in around 25% of the patients and cyclosporin failed to control macular edema in all patients included with this complication. When cyclosporin was used in combination with another immunomodulatory agent, the percentage of patients with inactive uveitis during the follow-up increased to around 50%.[63]

The use of cyclosporin as a monotherapeutic second line agent in the treatment of JIA-associated uveitis is not advised, but it could be used in combination with another second line agent.

The recommended dose of cyclosporin for the treatment of JIA-associated uveitis is <3mg/Kg/day separated in 2 equal doses.[51]

5. Leflunomide

Recently, a retrospective study looked into the efficacy of leflunomide versus methotrexate in the treatment of JIA-associated uveitis. A total of 15 patients were included, and a higher rate of uveitis flare-up was associated with the use of leflunomide.[64]

B. Biological Agents

Increasingly, children with uveitis refractory to topical corticosteroids, methotrexate and mycophenolate mofetil, or those who are intolerant of standard immunosuppressive agents are commenced on biological therapy. Biological agents are used to target and block the action of inflammatory cytokines or their receptors in order to prevent the autoimmune response. The biological agents most commonly used target TNFα, a pro-inflammatory cytokine which activates T cells. Other newer targets are CD20+ cells, interleukin receptors IL-2 and IL-6, and the B7 receptor on antigen presenting cells.

1. Infliximab

Infliximab is a chimeric (murine-human) monoclonal antibody administered by intravenous infusion which is repeated at 2 weeks and then every 4-8 weeks. Infliximab targets TNF-α,[65] the exact effect in biologic-induced apoptosis, cytotoxicity, and modulation of inflammatory cell trafficking remain unclear, however TNF antagonists in general act through two main mechanisms: those mechanisms mediated by TNF receptor (TNFR) blockage and those mediated by inhibitor binding to transmembrane TNF (tmTNF).[66] Given the results of several small observational studies, evidence suggests Infliximab may have a positive effect on reducing ocular inflammation.

Elevated concentrations of TNF-α in the serum and synovial fluid of JIA patients has been previously reported and reinforces the rationale of using anti-TNF-α for the treatment of JIA.[67] However the levels of TNF-α in serum do not correlate with the activity or severity of the disease.[68]

A retrospective analysis by Kahn et al. studied the use of high dose Infliximab (10-20 mg/kg/dose) on 17 children with refractory uveitis, 10 of whom had JIA. All 17 patients had a positive response. In 13 patients, there was no evidence of intraocular inflammation after 2 intravenous infusions. The remaining 4 required up to 7 infusions to achieve quiescence and visual acuity improvement. No side effects were reported.[69] However bearing in mind the short mean follow-up (13 months) in this study and the good outcomes in other studies using smaller doses of Infliximab, the higher dose of Infliximab treatment is not recommended by the authors.

Tynjala et al. evaluated the use of Infliximab and Etanercept in the treatment of chronic uveitis associated with JIA. Forty-five patients were enrolled. Of those taking Infliximab (3–6 mg/kg), 42% experienced improvement (decrease in number of anterior chamber cells), whereas 20% of those taking Etanercept improved.[70]

A small retrospective study by Sharma et al. undertaken in a clinical setting looked at 6 patients who took Infliximab (maximum dose 6 mg/kg) concomitantly with Methotrexate and corticosteroids. They noted 3 patients with JIA-associated uveitis entered drug induced remission and 2 had improvement of ocular inflammation. The corticosteroid dosage was able to be gradually reduced whilst receiving Infliximab, indicating a 'steroid-sparing role' for Infliximab. Infliximab was tolerated well in this study with no reported side effects.[71]

A study by Richards et al. supports the steroid-sparing role of Infliximab. 6 patients with JIA-associated uveitis were weaned off corticosteroids whilst on Infliximab. This study used a high dose of Infliximab, and all 6 patients experienced reduced ocular inflammation with no side-effects.[72]

In another study by Ardoin et al, 16 patients were treated with Methotrexate and median maintenance Infliximab (dose of 8.2 mg/kg) at a mean of 5.6 weeks intervals.

64% had complete control of ocular inflammation at 1 year, and 79% had no inflammation or a two-step decline in inflammation. Topical steroids were discontinued in 69%, and 58% remained free of uveitis recurrence at 1 year without any reported adverse event.[73]

One study looking into the safety of Infliximab in the treatment of JIA included 348 patients, where 214 were on treatment with Infliximab. The most commonly observed adverse events included mild infections, infusion or injection site reactions and alanine aminotransferase elevations. In this study no cases of malignancies or tuberculosis reactivation were reported. New-onset uveitis occurred in 9 patients, psoriasis or psoriasiform lesions in 13 and inflammatory bowel disease in 6.[74]

Infliximab is a chimeric antibody and the production of human anti-chimeric antibodies against Infliximab has been implicated in some anaphylactic reactions as well as the loss of effectivity over time.[75]

These small studies give a strong indication of the potential therapeutic role of Infliximab. However, as of yet no randomized controlled trials have been completed, so stronger evidence to support this is not available. Due to the lack of RCTs, the use of Infliximab is not approved for the treatment of JIA-associated uveitis and it is an off-label indication.

2. Adalimumab

Adalimumab (Humira) is a human monoclonal antibody against TNF-α. It has the advantage of being self-administered as a subcutaneous injection.

Zannin et al. looked retrospectively at the 91 patients with JIA-associated uveitis refractory to steroids, methotrexate and cyclosporin A listed in the National Italian

Registry. 48 received Infliximab and 43 received Adalimumab. Forty-seven patients (55.3%) achieved control of ocular inflammation, 28 (32.9%) had recurrent uveitis, and 10 (11.8%) maintained a chronic course. The remission rate was higher with Adalimumab (67.4% versus 42.8% with Infliximab; p = 0.025). No serious adverse events occurred, but 8 (8.8%) experienced 11 minor adverse events (9 with Infliximab, 2 with Adalimumab). These were infection (upper respiratory tract, herpes zoster and urinary tract infection), infusion reactions, and systemic symptoms such as headache, irritability and an urticarial rash. The latter adverse events were linked with the use of Infliximab in all cases. Ocular complications (cataracts, vitritis, cystoid macular edema and ocular hypertension) decreased from 0.47 to 0.32 per subject.[76]

Tynjala et al. performed a retrospective observational study of 20 patients with JIA-associated uveitis. 95% had tried previous anti-TNF-α therapy (Infliximab or Etanercept), were given 40mg Adalimumab every 2 weeks for a mean duration of 18 months. 35% showed improvement, 60% showed no change and 5% showed worsening of activity of uveitis. No serious side effects were seen in this study. The 35% who showed improvement were younger and had a shorter disease duration.[77].

Another retrospective analysis of 18 patients with JIA-associated uveitis administered 20-40mg Adalimumab every 2 weeks. Treatment of uveitis was defined by change in relapse rate: 'effective' treatment was classified as no relapse or >2 fewer relapses than before treatment. Treatment for uveitis was 'effective' in 88%. Arthritis (graded using the American College Rheumatology pediatric criteria) showed improvement in 81%. No adverse reactions were reported.[78]

The efficacy of Adalimumab has been evaluated in a recent study of 94 patients, 54 of whom had JIA-associated uveitis. The outcome measure was change in uveitis

activity measured using the Standardized Uveitis Nomenclature (SUN) criteria.[79] Uveitis significantly improved in 28% of patients (2-fold decrease in uveitis activity), and in this group corticosteroid drop usage was stopped in 31% and decreased to 1-2 drops/day in 35%. 16 (30%) experienced a moderate response, 16 (30%) had no response and 7 (13%) experienced worsening uveitis (a two-fold increase in uveitis activity). Improvement in arthritis was reported in those with JIA-associated uveitis: after 24 months, 27% had active joint disease, compared to 67% at the start. The dose of Adalimumab varied in this study as patients with a high degree of uveitis activity received weekly doses. The authors concluded Adalimumab clearly has a positive effect, and it potentially should be given in combination with Methotrexate.[80] Another small study by Tynjala et al. (n=21) showed similar results, with 53% showing improvement of ocular inflammation after Adalimumab. 19% showed no change, and uveitis activity increased in 26% of patients.[81]

Another study compared the efficacy of Adalimumab vs Infliximab in the treatment of chronic non-infectious childhood uveitis, which included 16 patients, 12 being diagnosed with JIA-associated uveitis. This study concluded that in the long term (3 years) Adalimumab had a higher uveitis remission than Infliximab.[82]

Current evidence would suggest that Adalimumab is beneficial in treating uveitis but so far studies have been small and do not provide strong evidence. Two large Phase III, randomized, double-blind, placebo-controlled, multicenter trials (The Sycamore Trial and the ADJUVITE trial) are currently underway. The Sycamore Trial is comparing the clinical effectiveness of Adalimumab in combination with Methotrexate versus placebo in combination with Methotrexate in patients with active JIA-associated uveitis refractory to only Methotrexate therapy. The results of this, expected in 2018, should shed light on the efficacy, safety and cost-effectiveness of

Adalimumab. (Accessed at http://www.sycamoretrial.org.uk/). The Independent Data Safety & Monitoring Committee (IDSMC) have recently reviewed the interim data and concluded there is enough data from 90 patients to support the use of Adalimumab in the treatment of JIA and Uveitis. The ADJUVITE trial (NCT01385826) is a study comparing the efficacy of Adalimumab versus placebo on reducing intraocular inflammation assessed by laser flare photometry after 2 months of treatment in patients with active uveitis in spite of combined treatment with topical steroids and Methrotexate.

Adalimumab has been reported as a relatively safe drug with few side effects. In general terms however, JIA-uveitis studies are limited by the size sample and duration of follow-up. Therefore the long-term safety of these treatments have been mostly assessed in rheumatology studies rather than uveitis studies. A large randomized controlled trial (n=284) using Adalimumab to treat Rheumatoid Arthritis found only 2 adverse events which occurred with 10% or greater frequency with Adalimumab than with placebo. The first was reactions occurring at the injection site such as erythema and/or itching, hemorrhage, swelling, or pain. These were reported in 21 (29%), 16 (23%), and 21 (29%) patients receiving Adalimumab 20, 40, and 80 mg respectively, versus 4 (6%) patients randomized to placebo ($p < 0.01$ v placebo for all comparisons). The second adverse event was hyperlipidemia (triglycerides >2.26 mmol/l). This was reported in 18 (25%), 22 (31%), and 22 (31%) patients receiving adalimumab 20, 40, and 80 mg respectively, versus 13 (19%) patients receiving placebo. Serious infections occurred in 4 (2%) patients taking Adalimumab. These were gastroenteritis, mild bronchitis, urinary tract infection and bacterial infection of unknown source with fever.[83] Smaller studies in the specific case of JIA have been also published regarding the safety of Adalimumab. A study in a German population

regarding the safety of Adalimumab in JIA found a rate of 50.9 per 100 patient-years of adverse events. Of which, only 11 were reported as serious (2.5 per 100 patient-years).[84] Another multicentric study in polyarticular JIA included 32 patients treated with adalimumab from 2 to 4 years of age. Severe adverse events were reported in 5 patients (16 %).[85]

Adalimumab is approved by the European Medicines Agency (EMA) for the use in active polyarticular JIA from 2 years of age and active enthesitis-related arthritis from 6 years of age.

3. Etanercept

The anti-TNF-α biologic Etanercept is a fusion protein produced through expression of recombinant DNA. Etanercept has been used successfully to manage JIA.[86] However, evidence from a number of small studies and a randomized control trial suggests it is less effective than other biologics at treating JIA-associated uveitis.

In 2005, Smith et al. conducted a small placebo controlled, double-blinded RCT looking at a cohort of 12 patients with JIA-associated uveitis. 7 patients received Etanercept twice a week (0.4mg/kg) and 5 took a placebo. They concluded there was no difference between Etanercept and the placebo, with 3 out of 7 in the Etanercept group and 2 out of 5 in the placebo experiencing reduced ocular inflammation ($p=1.0$). No serious adverse events occurred.[87]

A study suggested that rather than reducing ocular inflammation, Etanercept may precipitate endogenous uveitis. Six patients (3 of which had JIA), received 25mg of Etanercept twice a week for joint inflammation. A positive result was seen with

regard joint inflammation, but all 6 patients developed uveitis for the first time which resolved after changing to Infliximab.[88]

Another study looked into the results of 229 questionnaires completed by JIA patients taking Etanercept. Thirty-one patients (13.5%) had a history of uveitis before commencing Etanercept, and uveitis recurred in 19 of these patients whilst taking Etanercept. 2 other patients experienced uveitis for the first time.[86] The authors concluded the frequency and severity of uveitis seemed unaffected by Etanercept. Despite this evidence being rather weak, this remains in line with the results of the randomized control trial. Therefore, despite Etanercept being an effective drug to treat joint inflammation in JIA,[89] it does not have the evidence base for the treatment of JIA-associated uveitis.

Recently, a study including 3467 patients with JIA, showed that the rate of developing uveitis while on combination of Etanercept and methotrexate is similar than the rate in patients on methrotexate alone, for what seems unlikely that Etanercept may precipitate uveitis.[90]

Etanercept has been approved by the EMA for JIA in patients aged 2 to 17 years who have polyarthritis and extended oligoarthritis, adolescents aged 12 to 17 years who have psoriatic arthritis or adolescents aged 12 to 17 years who have enthesitis-related arthritis and have not responded adequately to or cannot take Methotrexate.

4. Golimumab

Golimumab has also been used to treat JIA-associated uveitis. Golimumab is a human monoclonal antibody targeting TNF-α licensed for use in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.

A 2011 case report states 40mg Golimumab every 4 weeks was effective in treating a case of JIA-associated uveitis refractory to all previous anti-TNF therapy. On taking Golimumab concomitantly with Methotrexate for 7 months, the patient entered remission.[91]

A set of 3 case studies from 2012 indicate that Golimumab can be used in cases of JIA-associated uveitis refractory to Infliximab, Etanercept and Adalimumab to achieve quiescence of inflammation to such an extent that surgery is possible. However in 1 case, arthritis and uveitis activity worsened despite Golimumab.[92]

The results of a phase III study to assess efficacy and safety of subcutaneous Golimumab in polyarticular JIA patients with active arthritis refractory to methotrexate have been preliminary reported. It showed a rapid response of active arthritis to the treatment with Golimumab. However it failed to meet the primary endpoint, as there was no significant difference in arthritis flare between the Golimumab and placebo group, after 12 weeks of open-label Golimumab.[A]

Further evidence regarding the use of Golimumab is required.

The use of Golimumab in JIA is off-label.

5. Rituximab

The CD20+ marker on B-cells has been indicated in the autoimmune process of JIA-associated arthritis. Rituximab, a chimeric monoclonal antibody targeting the CD20 marker, may be a useful treatment for JIA-associated uveitis.

Heiligenhaus et al. carried out a retrospective case series from 2011 used Rituximab in 10 patients who had uveitis refractory to corticosteroids, disease modifying anti-rheumatic drugs (DMARDs) and at least one anti-TNF. After one treatment course, 7

out of 10 patients had inactive uveitis and improved arthritis, although uveitis reoccurred in 3 of these within 6-9 months.[93]

A smaller study (n=8) concluded that following the use of Rituximab, refractory JIA-associated uveitis remained in remission in 7 out of 8 patients, with 5 patients being able to discontinue immunosuppressants and 2 discontinuing topical corticosteroids. No adverse events were reported.[94] These small studies suggest Rituximab could be beneficial for both refractory uveitis and arthritis.

The use of Rituximab in JIA is off-label.

6. Daclizumab

Daclizumab is a human monoclonal antibody to the IL-2 receptor of T-cells. It has been shown to be effective in treating adult uveitis, but there is little evidence regarding children.[95] An interventional prospective case series in 2009 trialed Daclizumab in JIA-associated uveitis. It looked prospectively at 6 children taking high dose Daclizumab for refractory uveitis. Four out of six had reduced active inflammation at week 12, however, 3 patients were withdrawn from the trial before the end of the study due to failure to control the intraocular inflammation, uncontrolled joint disease or side effects such as rash.[96] At present Daclizumab is no longer manufactured due to diminishing market demand and available alternative treatments.

7. Tocilizumab

Approved for treatment of arthritis, Tocilizumab is an anti-IL-6 receptor antibody. The only documented use of Tocilizumab for JIA-associated uveitis is a small study administering 8mg/kg every 4 weeks to 3 patients with refractory uveitis. 2 of the 3 responded and inactivity of uveitis was achieved, and in all 3 arthritis improved. No adverse events or side effects occurred.[97]

An open-label trial to assess the efficacy and safety of Tocilizumab in the management of JIA-associated uveitis refractory to other immunomodulatory treatments is currently recruiting patients in the USA (NCT01603355).

The use of Tocilizumab has been approved in children from 2 years of age with active systemic arthritis and polyarthritis.

8. Abatacept

Unlike other biologics, Abatacept is a soluble fusion protein that results in T cell inactivation by binding to CD80/CD86 on antigen presenting cells. It consists of the extracellular domain of human cytotoxic T lymphocyte antigen 4 (CTLA4) and the modified FC domain of human IgG1. Several case studies have indicated the role of Abatacept for treating JIA-associated uveitis, although no RCT has yet been performed.

A 2008 case report concluded that Abatacept (10mg/kg IV) induced remission of uveitis over a period of 12 months, with no adverse reactions or infections, and doses of concomitant medications were tapered off.[98]

Elhai et al. report two further cases. Both patients had JIA-associated uveitis refractory to at least 2 anti-TNFs. Treatment with Abatacept (10mg/kg IV), induced

remission. The two patients remained in remission for both uveitis and arthritis after 10 and 16 months. No drug reactions occurred.[99]

A final case report demonstrated that Abatacept induced remission of uveitis, yet not arthritis, in a 20 year old with refractory JIA-associated uveitis.[100] These results are mirrored in a small study in which 7 patients with JIA-associated uveitis refractory to at least 2 anti-TNFs were treated with 10mg/kg Abatacept monthly. Six out of seven achieved remission with no side effects after 9 months of treatment, but 1 patient withdrew due to arthritis flare and oral mycosis.[101]

A recent retrospective study included 21 patients with active JIA-associated uveitis treated with Abatacept after being refractory to at least 1 anti-TNF-α treatment. Uveitis control was achieved in 11 patients, but there was recurrence in 8 patients at the early follow-up and in the remaining 3 at later follow-up. Three patients developed new ocular complications while on Abatacept.[102]

Further studies with a higher number of patients are warranted to establish the real role of Abatacept in JIA-associated uveitis as the current reported evidences of efficacy are anecdotic.

Abatacept is approved in moderate to severe active polyarthritis in adolescents and children from 6 years of age who have not had a sufficient response to other medicines including one TNF blocker.

X. Bristol Eye Hospital Protocol

Patients who have complex uveitis and concomitant joint disease should be managed in a multidisciplinary clinic with senior ophthalmologists, rheumatologists and specialist nurses from a pediatric and ophthalmology background.

At present there is no approved treatment protocol for treating patients with JIA-associated uveitis in the United Kingdom. The following is a guide used at The Bristol Eye Hospital for the escalating treatment of these complex patients. It is based on current literature and clinical experience, although results of randomized controlled trials currently being undertaken will influence future treatment regimens.

Corticosteroid Drops

Children presenting with mild uveitis associated with JIA are started on the topical corticosteroid [PredForte (prednisolone acetate 1%)] 4-6 x a day, which is then tapered. Cyclopenolate 0.5-1% is used at night to reduce the risk of posterior synechiae formation. In our experience it is unlikely that children and their families will manage drops administered more than 4 drops a day for prolonged periods.

If after 3 months, control of intraocular inflammation has not been achieved (0-0.5+ cells in the anterior chamber according to SUN scale[79]) or more than 2 drops of steroid are required to control the uveitis (as the treatment with ≤3 drops daily of topical corticosteroid have been associated with an 87% lower risk of cataract formation compared with eyes treated with >3 drops daily[49]), or repeated prolonged courses of topical corticosteroids are required, escalation of treatment to systemic immunotherapy should be considered.

Methotrexate

Methotrexate is the immunosuppressant of choice in JIA-associated uveitis in view of its extensive use in managing children with JIA as described above. Methotrexate is used for children with uveitis who have failed treatment with topical steroids or who have active uveitis with ocular complications, such as a cataract. It is administered by

mouth or subcutaneously 10–15 mg/m^2 once weekly to a maximum of 20 mg oral or 25 mg by subcutaneous injection once weekly. It may take up to 3 months of treatment to take effect and although severe side effects are uncommon, they include bone marrow suppression as well as hepatotoxicity. Folic acid 5mg per week (administered on a different day to the Methotrexate) reduces the adverse reactions encountered.

If after 6 months of treatment with Methotrexate, control of intraocular inflammation has not been achieved, the switching of Methotrexate to Mycophenolate mofetil in those patients intolerant to Methotrexate could be considered. Little et al. demonstrated that the addition of a second immunomodulatory agent such as Mycophenolate mofetil did not showed substantial benefits but may lead to an increase in adverse effects,[103]. If there is a failure of the conventional immunomodulatory treatment after 3 months of treatment, escalating to biologic agents such as Adalimumab (Humira) is indicated.

Adalimumab

In the Bristol Eye Hospital, Adalimumab is currently accessed via the Sycamore trial or via NHS exceptional funding following suboptimal response to Methotrexate and/or Mycophenolate mofetil. We would advocate early escalation to a biologic such as Adalimumab in cases of uncontrolled disease despite the above treatment.

Adalimumab is administered by subcutaneous injection. A dose of 24 mg/m^2 (max. 40 mg) on alternate weeks is used in children aged 4-12 years old and 40 mg on alternate weeks is used in children aged 13-17 years old, with review if there is no treatment response within 12 weeks.

In exceptional cases where the combination of Adalimumab and Methotrexate fails to control the ocular inflammation, Infliximab is considered, with the second infusion at 2 weeks and then 6 and 8 weekly. In the cases of poor response shorter intervals including 4 and 6 weeks periods could be considered.

In cases were Infliximab is not adequate also to control the intraocular inflammation other therapies such as Tocilizumab or Abatacept are considered.

XI. Assessing Response

The multinational interdisciplinary working group for uveitis in childhood proposed a standardized outcome measurement for clinical trials in JIA-associated uveitis. Consensus was reached that clinical outcomes should be reported at defined time points in longitudinal studies and patients should be stratified by prognostic markers. Visual acuity testing should be age appropriate. The severity of uveitis should be measured as anterior chamber cell grade according to the criteria of the SUN working group,[79] and duration of active inflammation should be recorded. Visually significant structural complications should be documented and quantified with standard measures and treatment response, as well as corticosteroid-sparing achievement, should be detailed. Age-specific quality of life questionnaires are recommended.[104]

The use of 'Laser flare photometry' has been proposed as it may provide a more accurate way of assessing response to treatment. This is an objective quantitative method that enables accurate measurement of aqueous flare and cells with high reproducibility. Laser flare photometry allows detection of subclinical alterations in

the blood–ocular barriers, identifying subtle pathological changes that could not have been recorded otherwise.[105]

XII. Treating Complications

Long-standing inflammation can lead to sight threatening complications, which must be treated alongside the uveitis.

The presence of ocular complications (such as band keratopathy, posterior synechia, cataract, ocular hypertension/glaucoma, hypotony, epiretinal membrane, optic nerve edema, macular edema or vitreous opacity) at presentation is estimated between 45-67% with JIA associated uveitis.[25; 106] The Systemic Immunosupressive Therapy for Eye Disease Study (SITE), in a cohort of 327 patients with JIA-associated uveitis, showed that 60% of the eyes had at least 1 ocular complication at the presentation. The incidence of developing new complications was estimated to be 0.15/eye-year, and this rate was lower (0.04/eye-year) in those cases that did not have complications at presentation.[107] There is a higher risk of developing complications among those patients with severe disease at onset,[45] posterior synechiae, active anterior chamber inflammation >1 + cells, and previous intraocular surgery.[107] Male gender has also been associated with the development of complications and poor outcomes.[108; 109]

The most frequent complication is cataract, although some reports established a higher frequency for band keratopathy and posterior synechiae.[28; 106] Significant risk factors for the development of cataract included posterior synechia, active intraocular inflammation, and topical corticosteroid use at presentation.[49]

Band keratopathy can be eliminated by chelating agents or laser surgery, but Najjar et al. found that after EDTA chelation, recurrence was common (60%) in cases of uveitis.[110; 111]

For cataracts, standard phacoemulsification and intraocular lens (IOL) implants are indicated. Although the IOL implantation has been controversial, there is increasing evidence that this is a safe procedure with current surgical techniques.[112] However Magli et al. reported a higher incidence of secondary glaucoma in patients undergoing primary IOL implantation compared to secondary implantation.[113] In our unit, we use an aggressive pre- and post-operative course of topical and systemic corticosteroids, such as IV methylprednisolone and systemic prednisolone. Ideally both eyes should be free of inflammation for 3 months prior to surgery.[114; 115; 116]

Increased ocular pressure secondary to the inflammation and/or steroid use is treated with topical antihypertensives. If the response is poor and raised IOP and secondary glaucoma persists, trabeculectomy or drainage tube surgery may be considered.[115; 117; 118] A recent study investigating the use of goniotomy in the treatment of childhood uveitis glaucoma, which included 20 patients with JIA, reported promising results in the use of this technique with 15 of 35 patients requiring no further surgery.[68]

Macular edema may be treated with systemic corticosteroids, local corticosteroids and potentially an anti-VEGF agent such as bevacizumab (Avastin). Mackensen et al. found intravitreal bevacizumab to be an effective and safe treatment although the effect may be transient, and re-injections may be necessary.[119; 120]

XII. Method of Literature Search

A search of the MEDLINE database was performed by using the PubMed website for the years 1966 through 2013, inclusive. The search terms employed were uveitis,

iritis, iridocyclitis, epidemiology, juvenile idiopathic arthritis, juvenile chronic arthritis, juvenile rheumatoid arthritis, and juvenile arthritis. All articles considered to be of clinical significance taken into account. Main emphasis was laid on articles from recent years. The bibliography of each publication was reviewed for articles not captured by the MEDLINE search. Those articles which included additional information and were considered to be of clinical importance were included.

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