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Ocular Involvement in Juvenile Idiopathic Arthritis: Classification and Treatment

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Abstract Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases in childhood with a prevalence of 4 in 1,000 children. Anterior uveitis is a well-known threatening comorbid condition of JIA and affects around 10 % of the patients depending on JIA subtype. A large proportion of children with JIA develop uveitis in the first year of disease and 73 to 90 % after 4 years. Uveitis can progress into adulthood and usually occurs as 'white uveitis', while in the JIA related to the enthesitis subtype that is symptomatic. Current studies reinforced the previous observations that early age of JIA onset, oligoarticular subtype and ANA reactivity are the main risk factors for the development of uveitis. Factors associated to worse prognosis are as follows: findings of 1+ or more vitreous cells at presentation and initial visual acuity of 20/200 or worse. The Standardization of Uveitis Nomenclature (SUN) Group took the first step to define outcome measures for uveitis, but it was established for adults. The Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC) proposed outcome measures for JIA-associated uveitis incorporating the SUN criteria in 2011. The current suggested management recommends to start early a steroid-sparing effective immunomodulatory systemic treatment. Methylprednisolone intravenous pulse therapy, rituximab, tocilizumab and abatacept are promising agents. Because JIA-associated uveitis is a potentially threatening comorbidity, it is important to recognize and treat it early to prevent any visual damage that could impair visual acuity.

Keywords Juvenile inflammatory arthritis · Uveitis · Anti-TNF

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Introduction

JIA is one of the most common rheumatic diseases in childhood with a prevalence of 4 in 1,000 children [1] and classified in subgroups according to the ILAR criterion [2].

Anterior uveitis is a threatening comorbid condition of JIA that affects around 10 % of the patients depending on subtype. Before the methotrexate era, uveitis was more prevalent, up to 38 %. Nowadays, methotrexate is started early in the course of JIA to treat the arthritis itself, and indirectly, it suppresses the development of uveitis.

Uveitis is a chronic non-granulomatous inflammation of the anterior chamber of the eye, affecting the iris and ciliary body. The onset is usually insidious and mostly asymptomatic, but uncontrolled uveitis is one of the most common causes of blindness in the Western world. When it occurs, it develops in the first year of disease in 73 % of the patients and in 90 % after 4 years after the onset of arthritis [3]. Around 12 % of patients present with uveitis before the onset of the arthritis [3], and the median time of uveitis onset after the arthritis is 5.5 months.

Uveitis can continue into the adulthood, as was shown in a recent retrospective study of 154 adolescents [4], where 18 % of these patients had uveitis and 8 % still had its active form in the last year of follow-up.

Uveitis seems to have a bimodal activity curve, a first peak in early childhood and the second one around 13–14 years of age [5] and often does not achieve remission even in the adulthood.

It occur as 'white uveitis' when it is not associated with redness and pain as opposed to the form seen in the JIA related to enthesitis subgroup that is symptomatic. Regular ophthalmologic screening is recommended depending on age of onset and disease subtype [3, 6, 7].

Risk Factors for Developing Uveitis

Early age of disease onset, oligoarticular pattern, ANA positivity and European ancestry are the main risk factors for the development of uveitis [1–4, 8–12]. In a study from Cole et al., a history of psoriasis also appeared to be an additional risk factor for uveitis [9]. Based on these risk factors, the screening programmes to detect uveitis early are reinforced [3, 11] (Table 1).

Risk Factors to Develop Chronic Severe Uveitis

In a recent publication [12], 990 eyes of 687 patients with new onset autoimmune anterior uveitis were reviewed. Factors associated to lower remission rate were as follows: diagnosis of JIA, findings of 1+ or more vitreous cells at presentation and initial visual acuity of 20/200 or worse. Patients with these risk factors seem to have a higher risk of persistent inflammation and would need early intervention with an effective immunosuppressive treatment scheme.

Another recent study [13] with similar results added additional risk factors for the development of severe uveitis and significantly decreased visual acuity (VA). They studied 596 affected eyes of five tertiary uveitis clinics in the USA. At presentation, 240 eyes (40.3 %) had a VA of ≤20/50 (over half decreased eye resolution), 144 eyes (24.2 %) had a VA of ≤20/200 (10 % of normal eye resolution) and 359 eyes (60.2 %) had at least one ocular complication. The incidence for development of one more complication was 0.15 eye/year; however, in eyes, who had no complication at presentation, this number was significantly lower with 0.04 eye/year. In the course of the disease, prior eye surgery, posterior synechia and active uveitis were statistically significantly associated with loss of VA (Photo 1). . Increased anterior chamber cell grade was associated with increased rate of visual loss and the use of immunosuppressive drugs were associated with less visual loss, particularly for the ≤20/50 outcome ($p<0.01$), showing that effective immunosuppressive treatment can prevent damage.

How to Assess the Outcome of Uveitis?

Currently, there is no valid definition of remission in JIA-associated uveitis. According to the Wallace criteria [14], 'no active uveitis' is included as an item but with the remark that 'no active' has to be defined. Most studies performed prior to the establishment of the Standardization of Uveitis Nomenclature (SUN) criteria used their own outcome measures. The SUN Group took the first step to define outcome measures for uveitis [15] but focusing in adult patients only. The following items were defined by nominal group technique: unified classification of an anatomic classification of uveitis, descriptors of uveitis, grading of the anterior chamber cells, grading of the anterior chamber flare, grading scheme for the activity of uveitis, definition of complication of uveitis and how to report these complications. The grading of the activity is not adapted to the classical cell numbers of classical JIA-associated uveitis (personal communication by the paediatric ophthalmologist Clive Edelstein at the a consensus meeting in Barcelona, 2012).

To establish specific outcome measures for JIA-associated uveitis, the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC) was established. This group consists of paediatric rheumatologists and ophthalmologists with special interest in JIA-associated uveitis. The first proposal for a set of outcome measures was published in 2012 [16]. This proposal reflects the result of a Delphi process where items were ranked regarding assessment of outcome of JIA-associated uveitis and a consensus meeting was held in 2009, where with a nominal group technique, a consensus was

Table 1 Suggested screening intervals for JIA-associated uveitis in patients, who did not had uveitis—adapted and slightly modified from the published version of Heiligenhaus et al. [2]

JIA subtype	Age at onset (years)	JIA duration (years)	Recommended screening intervals in months
Oligoarticular; RF negative polyarticular; psoriatic; other arthritis	≤6	≤4	3
Oligoarticular; RF negative polyarticular; psoriatic; other arthritis	≤6	≥4	6
Oligoarticular; RF negative polyarticular; psoriatic; other arthritis	≤6	≥7	12
RF negative polyarticular; psoriatic; other arthritis	≥6	≤2	6
RF negative polyarticular; psoriatic; other arthritis	≥6	≥2	12
Enthesitis associated	Not applicable	Not applicable	12
RF positive polyarticular	Not applicable	Not applicable	12
Patients with uveitis	Not applicable	Not applicable	According the uveitis course

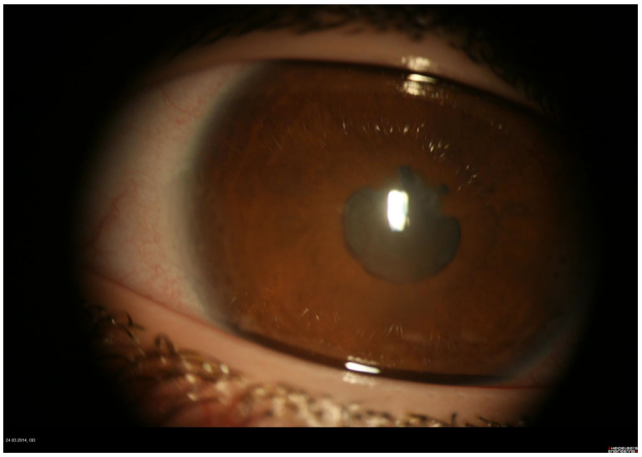

Photo 1 Eye with synechia in a JIA patient (courtesy of Prof A. Heiligenhaus, Münster, Germany)

reached regarding a set of proposed outcome measures. These items not only incorporated the SUN criteria but also included other aspects of the outcome, as number of visits with active uveitis, occurrence of new structural damage, quality of life, overall uveitis-related disability, social outcome, anti-inflammatory medication, surgery and biomarkers. Some of these items are experimental; as until the present time, no validated biomarker exists; we still do not have universal validation in several languages of uveitis-specific quality-of-life instruments. The members of the MIWGUC Group are currently prospectively validating these parameters.

Do We Have Validated Biomarkers?

Ayuso et al. [17] showed in a pilot study that transthyretin was elevated on the aqueous humour of JIA-associated uveitis patients. The transthyretin as a nascent protein has a molecular weight of 15.88 kDa. Well-known systemic functions of transthyretin are responsible for the transport of thyroid hormones and of the retinol-binding protein. Unfortunately, this only can be assessed in an intraoperative set-up, so it cannot be used in a daily routine to assess activity in uveitis and has to be prospectively evaluated.

A pilot study from another group, which was published only as an abstract, searched for a uveitis marker in 13 JIA patients, and found several interesting potential candidates, like rheumatoid factor, cytokines and T cell receptor alpha chain, anti-CD40 single-chain antibody fragment, A 49, clusterin, as well as anti-tumor necrosis factor (TNF) light chain Fab' fragment that could be detected in the lacrimal secretion [18]. In this pilot study, a correlation of the level of these proteins with activity of uveitis was not evaluated. A reliable biomarker in the tear would be a real breakthrough, as it is easily accessible and could measure the activity of JIA-associated uveitis.

What Is the Best Treatment for JIA-Associated Uveitis?

Current Guidelines

In this section, I will review the systemic pharmacologic treatment of uveitis. The treatment is often started and monitored by a paediatric rheumatologist in a teamwork effort with the ophthalmologist. Several reports in the ophthalmologic literature concentrate on the local treatment of JIA-associated uveitis [19, 20]. Based on the German therapeutic guidelines for JIA-associated uveitis [21], local treatment has a role when the disease is mild and when it can be weaned off fast. The local treatment is mainly with topical corticosteroids; therefore, using it for 3 months or longer is associated with significant long-term side effects.

According to the guidelines, if after 12 weeks of local treatment the corticosteroids eye drops cannot be reduced to three or less per day or systemic corticosteroids cannot be reduced to less than 0.15 mg/kg body weight after 4 weeks of therapy, systemic treatment with methotrexate (10–15 mg/m^2/week orally or subcutaneously) or azathioprine (2–3 mg/kg/day orally) should be started. Methotrexate is the first choice since azathioprine is not effective for arthritis. If no inactivity of uveitis is reached after 3 to 4 months of disease-modifying anti-rheumatic drug (DMARD) therapy, adalimumab 24 mg/m^2/every 2 weeks subcutaneously, or infliximab 3–10 mg/kg intravenously every 4–8 weeks, or cyclosporine A 3 mg/kg/day can be started. The evidence behind cyclosporin A efficacy is the weakest [22]. There were no suggestions published for patients who failed to respond to anti-TNF therapy. These treatment guidelines were based on the literature published until 15th of November 2009 and were established on cases series, with no randomized controlled studies.

The current philosophy supporting the treatment of JIA-associated uveitis is founded on no tolerance for active uveitis, in addition to no tolerance for chronic corticosteroid use, either locally or systemically.

Recently Published Data

There is new data published after the establishment of the mentioned guidelines, which favours certain medications. A current meta-analysis regarding the efficacy of methotrexate showed that 73 % of the patients responded well [23]; it should be noted that all the evaluated studies were not controlled. In a single-centre case series including eight patients that were non-responsive to immunosuppressive drugs, like methotrexate and mycophenolate mofetil, and nine patients non-responsive to other anti-TNF, like infliximab and etanercept, when adalimumab was started, at 3 months, 50 % of the patients responded, utilizing the SUN criteria

[24]. In another single-centre study with ten JIA-associated uveitis patients, receiving adalimumab, applying the SUN outcome criteria, 60 % of the patients were considered responders [25]. Interestingly, in another case series, where adalimumab was initiated 7 months after the onset of uveitis, a remission rate of 76 % was reached and the number of anterior uveitis flares before adalimumab that was reported to be 1.6±0.4/year decreased to 0.7±0.3/years ($p<0.001$) [26]. Suggesting earlier initiation of an effective treatment leads to a better remission rate. This is also shown in other publications, where using a combination therapy of two DMARDs in 6 of the 13 cases treated with adalimumab, after a mean time of 4 years from the uveitis onset, only a 42 % remission rate could be reached [27], compared to 76 % when it was initiated in the mean time of 7 months after the onset of uveitis [27]. This demonstrates that the effective therapeutic window of opportunity is early in the disease course.

The effectiveness of adalimumab (24 mg/m^2) and infliximab (5–10 mg/kg per dose, at 0, 2, 6 and then every 6–8 weeks) was compared, and adalimumab seemed to be more effective [28, 29]. In the subgroup analysis of the nine JIA patients, under adalimumab treatment, there was a higher probability of remission and a longer period of time in remission. These findings were confirmed by the National Italian Registry [30], where a remission rate of 67.4 % was obtained with adalimumab versus 42.8 % with infliximab ($p=0.025$). In the first placebo-controlled trial designed for patients with JIA-associated uveitis, who did not respond to 12 weeks of methotrexate treatment (10 to 20 mg/m^2/week), adalimumab (20 mg/every 2 weeks under 30 kg of bodyweight or 40 mg/every 2 weeks by sub-cutaneous route over 30 kg of body

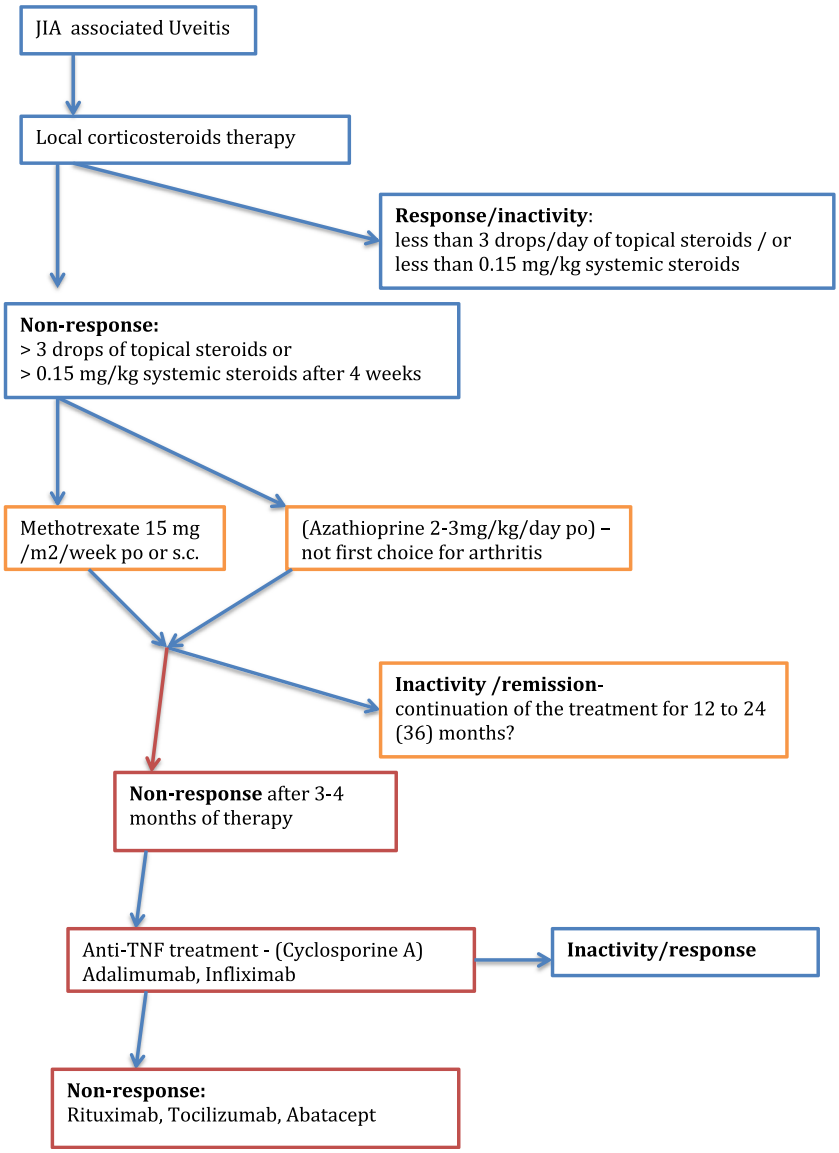

Fig. 1 Suggested therapeutic flow sheet of JIA-associated uveitis based on current data

weight) or placebo is given. The results of this placebo-controlled trial are still pending [31].

Rescue Therapy or New Second-Line Agents?

According to the previous mentioned data, around 30 to 40 % of the patients did not achieve remission under adalimumab or switching between anti-TNF therapies when added to methotrexate or mycophenolate mofetil. The question that comes up is what kind of rescue therapy could be offered? Rituximab seems to be promising.

Rituximab is a chimeric human-mice monoclonal antibody directed against the CD20 surface marker, localized on pre-B lymphocytes. In a pilot study with ten JIA non-responsive patients to a combination of DMARD and anti-TNF agent, rituximab was given and seven of the ten patients reached inactivity of uveitis [32].

Another promising rescue agent is tocilizumab, an anti-interleukin-6 (IL-6) receptor antibody. In a pilot case series, three patients who had already failed therapy with DMARDs plus at least one anti-TNF were treated with tocilizumab, and two of the three patients responded [33]. Tocilizumab seems to be a promising effective agent to treat JIA-associated uveitis [34, 35].

Abatacept, a selective T cell co-stimulation modulator, showed a positive effect as a rescue therapy in resistant uveitis as it was given to seven patients with an average of 11.6 years in duration of uveitis that did not respond to DMARDs and at least two anti-TNF agents. All patients responded and six maintained clinical remission after 9.2 months of follow-up [36]. Other successful case reports with the use of abatacept for uveitis in JIA are supporting this impression [37–39]. It was thought that anti-interleukin-17 therapy (secukinumab) would be an option, but it was proved to be ineffective [40].

Rituximab, tocilizumab and abatacept could be used in the future as second-line agents after methotrexate failure. It would be important to identify a biomarker, which would predict what kind of cytokine blockade that would be most effective.

From a ‘non-biologic therapy’ perspective, methylprednisolone intravenous pulse therapy is an option [41] to suppress active inflammation, until a biologic therapy can be offered, as all of these biologic therapies are currently off label and the coverage of the cost of this treatment is different around parts of the world.

Is It Possible to Predict Which Patient Will Relapse?

Patients who received a systemic immunomodulatory treatment earlier in the course of uveitis and were younger at the time of initiation of the immunomodulatory treatment had higher remission rates [26, 42]. Actually, these two factors overlap, as most patients with severe uveitis are of younger age. In the study by Ayuso et al., relapse-free survival correlated with more than 3 years of treatment with methotrexate (MTX), before discontinuation of MTX, patients age at discontinuation, patients who were older than 8 years of age at time of withdrawal, duration of inactive disease under medication and in patients who had inactivity of uveitis longer than 2 years before withdrawal of MTX [43].

It was demonstrated that younger patients who received immunomodulatory treatment earlier in the course of uveitis [31] had a higher remission rate. The two factors overlap, as most patients with severe uveitis are of younger age. More observations and studies are needed to identify other predictors.

Conclusion

JIA-associated uveitis is a potentially severe comorbidity of JIA that can have a significant impact in the patient’s quality of life. It is important to recognize it at the earliest possible stage and provide treatment promptly in order to prevent any damage that will irreversibly interfere with the visual acuity (Fig. 1).

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