Diagnosis and treatment of uveitis associated with juvenile idiopathic arthritis

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Abstract

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in pediatric population, with uveitis as the most common and severe extra-articular manifestation. Eye damage (bilateral in 70-80% of cases) is usually anterior, chronic and asymptomatic. Young age, female gender, oligoarticular form and ANA positivity are risk factors for chronic anterior uveitis (CAU). Acute anterior uveitis (AAU) frequently occurs in HLA-B27 positive boys with enthesitis-related arthritis. The onset is on average 1.8 years after the onset of JIA, but it may also precede the articular manifestations. Ophthalmological screening for JIA is recommended every 3 or 6-12 months depending on the combination of risk factors for associated uveitis. The major purpose of the treatment is to minimize the loss of visual acuity. The treatment is topical (corticosteroids, cycloplegics) and systemic (short-term glucocorticoids, methotreexate, biological drugs). Biological therapy (indicated if previous treatments are ineffective) is using anti-TNF drugs as first choice (most studies are indicating sup erior efficiency for Adalimumab). Usually AAU is treated promptly and no systemic treatment is needed. In some cases the evolution of CAU can lead to severe complications (synechiaes, cataract, glaucoma, even blindness). Interdisciplinary approach involving the pediatric rheumatologist and ophthalmologist is essential for correct monitoring of this disease.

Keywords: uveitis, juvenile idiopathic arthritis, biological treatment

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Background

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children, with an incidence of 8.2 (7.5-9)/100,000 in the pediatric population younger than 16 years. The annual prevalence is approximately 70.2 (16-140)/100,000. Uveitis is the most common and most severe extra-articular manifestation of JIA, accounting for 15-67% of all causes of uveitis in children [1,2]. Chronic anterior uveitis (CAU) occurs in about 10-20% of JIA patients, while acute anterior uveitis (AAU) develops in 2-4% of JIA patients [3,4].

Diagnosis, classification, symptoms

The diagnosis of uveitis is made based on the inflammation elements detected by slit lamp examination. These include the presence of cells in the anterior chamber of the eye and the flare resulting from rupture of the blood-aqueous barrier, with leakage of serum proteins into the vitreous body. *The Standardization of Uveitis Nomenclature* (SUN) criteria [2] allow: a. *Determining the anatomical localization* of uveitis: uni- or bilateral; anterior, intermediate, posterior or panuveitis; b. *Specifying the time course* of uveitis: acute, subacute, chronic or recurrent; c. *Staging* the intraocular *inflammation* and monitoring its progression. In about half of the patients with JIA-associated uveitis, eye damage occurs shortly before the onset of articular manifestation or in the first 3 months after the onset of arthritis [5-8], with 90% of these patients developing

uveitis in the first 4 years after the onset of arthritis. Ocular involvement is bilateral in 70-80% of the cases [5,9-12]. Patients with unilateral disease in the first year are unlikely to develop bilateral uveitis afterwards. In most cases, the onset is with anterior uveitis, although some cases may evolve into panuveitis. JIA-associated uveitis is usually anterior, chronic/recurrent and asymptomatic and occurs mostly in (persistent and extended) oligoarticular JIA. Symptomatic AAU can be detected in some cases, more frequently in boys with HLA-B27-associated disease such as spondyloarthropathies (enthesitis-related arthritis or psoriatic arthritis) [1]. AAU differs from CAU in that AAU is episodic, unilateral, with a sudden onset characterized by eye pain, conjunctival congestion, photophobia, headache and visual disturbances. Until an ophthalmological examination is performed, the symptoms are usually attributed to an acute infection, a foreign body or an allergic condition [8]. Usually, AAU requires no systemic treatment.

Differential diagnosis of JIA-associated uveitis

Arthritis-associated uveitis requires a wide range of differential diagnoses [8]: a. Arthropathy associated with inflammatory bowel disease. b. Infections: Reiter's syndrome (reactive arthritis, urethritis, conjunctivitis), cat-scratch disease, Herpes simplex virus infection, Epstein-Barr virus infection, HIV infection. c. Rheumatic diseases: JIA (oligoarticular, polyarticular, psoriatic, enthesitis-related arthritis), less often systemic lupus erythematosus or polyarteritis nodosa. d. Vasculitis: Kawasaki disease, Behcet disease, Henoch-Schonlein-purpura, granulomatosis with polyangiitis. e. Other diseases: tubulointerstitial nephritis with uveitis, sarcoidosis, Blau syndrome, chronic infantile neurological, cutaneous and articular (CINCA) syndrome.

Some studies have found that the onset of associated uveitis took place on average 1.8 years after the onset of JIA [4]. However, in 8-10% of the cases, uveitis may precede the diagnosis of JIA, so that asymptomatic ocular inflammation may progress without being diagnosed for significant periods of time, with ocular involvement being detected during a routine eye examination at the stage of irreversible complications. Other studies have suggested a biphasic evolution with a second peak of disease activity at puberty, suggesting the need for long-term active monitoring of the patients with uveitis [13]. The factors inducing an acute or insidious onset of the two forms of uveitis are currently unknown.

Some risk factors for the development of JIA-associated uveitis have been identified, namely: sex, type of JIA, age at disease onset, antinuclear antibodies (ANA) positive or HLA-B27 positive. Young age, female gender, oligoarticular form and ANA positivity are risk factors for CAU. In contrast, HLA-B27 positive boys with enthesitis-related arthritis are at an increased risk of AAU [2,14-17].

Ophthalmological screening

The American College of Rheumatology Guideline for the screening, monitoring, and treatment of JIA–associated uveitis [3] made the following recommendations:

a. Ophthalmological screening every 3 months for JIA with high risk of developing associated uveitis: oligoarthritis, rheumatoid factor (RF) negative polyarthritis, psoriatic arthritis or undifferentiated arthritis – in ANA positive children, age at onset under 7 years old, during the first 4 years of evolution of arthritis.

b. Ophthalmological screening every 6-12 months (depending on the combination of risk factors) **for JIA with intermediate or low risk of developing associated uveitis:** a. oligoarthritis, RF negative polyarthritis, psoriatic arthritis or undifferentiated arthritis – in ANA negative children, age at onset over 7 years old, after the first 4 years of evolution of arthritis; b. systemic, RF positive polyarticular JIA, enthesitis-related arthritis; c. any form of JIA associated with the HLA-B27 positive genotype.

Treatment of JIA-associated uveitis

The primary goal of the treatment of JIA-associated uveitis is to minimize the loss of visual acuity, i.e. to have 0 cells in the anterior chamber of the eye bilaterally (which is rarely possible in practice). Active JIA-associated uveitis requires immediate treatment.

A. JIA and active associated uveitis

1. Topical corticosteroids. Therapy is initiated when the grading of cells in the anterior chamber of the eye is > 0.5, when there is evidence of fibrin in the anterior chamber and pigmented keratic precipitates with corneal edema and decreased visual acuity [2]. Topical glucocorticoids should be used as short-term therapy for up to 3 months [3]. Prednisolone acetate 1% (with superior corneal penetration) or dexamethasone phosphate 0.1% are the first-line treatment for CAU and AAU. The daily doses are prescribed by the ophthalmologist depending on the degree of inflammation [1]. Initial doses of Prednisolone acetate 1% higher than 1-2 drops/eye/day may be required but the risk of ocular complications (glaucoma, cataract) is high. Frequent administration (every 1-2 hours) is initially used in order to quickly control the inflammation and doses will be reduced when the cellularity of the anterior chamber returns to normal. In the case of active uveitis, the introduction of topical glucocorticoids or the short-term increase of topical doses are preferable to the introduction of systemic corticosteroids. Prednisoloneacetate in a dose of 1-2 drops/day can sometimes be used as monotherapy only if there are no signs of ocular complications (glaucoma, cataract) and if monthly monitoring by the ophthalmologist is possible [3]. Periocular and intraocular injection is decided by the ophthalmologist. Cycloplegics (tropicamide or cyclopentolate 0.5–1%) are administered topically to prevent the formation of synechiaes by their

midriatic effect [2].

2. Topical or systemic non-steroidal anti-inflammatory drugs (NSAIDs) have no proven effect as monotherapy, but can be used as adjunctive therapy [1].

3. Systemic immunosuppression is recommended from the time of diagnosis in active JIA-associated uveitis if there are negative prognostic factors: posterior synechiaes, band keratopathy, glaucoma, cataract, decreased visual acuity, hypotonia, macular edema, dense vitreous opacification [1]. In the absence of active uveitis, cataract, glaucoma, synechiaes or band keratopathy do not require anti-inflammatory treatment [2]. Systemic immunosuppression is also indicated in cases that do not respond to topical therapy or in which uveitis is reactivated as the doses of topical glucocorticoids are reduced [1]. The initiation and monitoring of systemic immunosuppression can be performed by a physician (pediatric rheumatologist, rheumatologist or ophthalmologist) with experience in the administration of this medication and in monitoring for side effects.

a. Methotrexate (MTX) is the first-line systemic immunosupresive drug. The usual dose is the one used in JIA-associated arthritis, i.e. 15 mg/m^2/week, with folic acid supplementation. At the beginning of MTX therapy, better results can be obtained by subcutaneous administration [3]. Indications: a. In cases that do not respond after 12 weeks of topical therapy; b. In patients who require more than 2 topical glucocorticoid drops per day for the control of JIA-associated uveitis; c. If under treatment with topical corticosteroids the inflammation progresses or ocular complications occur.

b. Other disease modifying anti-rheumatic drugs (DMARDs) (leflunomide, mycophenolate mofetil, tacrolimus, azathioprine, cyclosporine) are used as alternative therapies in patients who have not tolerated MTX therapy or in cases of resistance to MTX associated with biological therapy. Mycophenolate mofetil is a potential alternative to biological therapy in the presence of active uveitis without active arthritis [2].

c. Systemic glucocorticoids are used with caution and for short-term in children, due to the multiple side effects of long-term corticosteroid therapy (especially growth suppression and osteopenia). However, systemic glucocorticoids are useful in the rapid control of intraocular inflammation (severe forms of uveitis or macular edema). Pulse therapy with methylprednisolone (20-30 mg/kg/day for 1-3 days) or Prednisone (1-2 mg/kg/day) can be used. Control of ocular inflammation can be obtained after 10-20 days, from which time the dose of systemic cortisone should be reduced. The recurrence of signs of ocular inflammation during cortisone withdrawal requires association with other immunosuppressive drugs, which is a preferable option to the resumption of corticosteroid therapy in high doses [2].

d. Biological therapy is indicated if therapy with MTX or other DMARDs (disease-modifying anti-rheumatic drugs) is ineffective (grade 0 cellularity is not obtained in the anterior chamber of the eye after 3 months of treatment) or poorly tolerated (in the latter case biological treatment is accepted as monotherapy). Some experts recommend that in severe CAU (with evidence of structural complications secondary to uveitis or to topical steroid therapy), as well as in complications that threaten the irreversible loss of visual acuity, the simultaneous initiation of the combined use of MTX + biological therapy is required from the start [18]. The anti-TNF (anti-tumor necrosis factor) drugs are of first choice: adalimumab, infliximab, golimumab. Of these, most studies indicate adalimumab as first choice therapy in JIA-associated uveitis [1,19-27]. Etanercept therapy was associated with a high relapse rate and an increased risk for developing flares. For these reasons, expert groups do not recommend etanercept as biological therapy in JIA-associated uveitis [1,3]. If biological therapy is ineffective (after a minimum recommended time interval of 3 months), experts recommend dosing the serum levels of the drug and detecting the anti-drug antibodies. If the patient does not have such antibodies but has low serum levels of the drug, some studies recommend increasing the doses above standard (e.g. Infliximab 20 mg/kg) or reducing the interval between doses (e.g. weekly Adalimumab) [1,3]. If again no therapeutic response is obtained, a switch with a second anti-TNF is recommended. If not even the second anti-TNF gives response, using a biological drug with a different mechanism of action (tocilizumab, rituximab or abatacept) may be considered [1,3].

B. Patients with JIA and CAU who require long-term (at least 3 months) treatment with 1–2 drops/day of prednisolone acetate 1% (or the equivalent) for the control of JIA-associated uveitis [3]**.** If by that time patients have received only topical treatment, systemic therapy (MTX) will be initiated to allow interruption of topical corticosteroid therapy (high doses and long-term intraocular cortisone administration have an increased risk of glaucoma and cataract). If patients are already under systemic therapy, it is recommended to change the systemic immunosuppressive therapy or to increase the dose of the administered drug.

C. Patients who develop new active CAU despite stable systemic therapy. In the case of short-term reactivation of controlled uveitis, dose escalation or switching of systemic therapy is not recommended in the first phase, but doses of topical corticosteroids may be added or increased for short periods. AAU episodes are typically of short duration and can be easily controlled with topical corticosteroids, while maintaining the previous immunosuppressive therapy. If reactivations are frequent or there is dependence on topical corticosteroid therapy, changing the biological drug may be considered [3].

D. Dose reduction recommendations. There is currently no unanimously accepted definition of inactive disease valid for JIA-associated uveitis. The main purpose

of the treatment is the clearance of cells from the anterior chamber of the eye. However, the presence of macular oedema, ocular hypotonia or rubeosis iridis may require anti-inflammatory treatment even in the absence of cells in the anterior chamber [1]. The duration of administration of systemic therapy (DMARDs/biological therapy) has not been established. Most consensus guidelines indicate at least 2 years of inactive uveitis (requiring no topical corticosteroid therapy) and inactive arthritis before stopping systemic therapy [2,3]. In patients with JIA and CAU controlled with systemic therapy but dependent on topical steroids, reduction of topical steroid doses (increased risk of local complications) is a priority over reduction of systemic therapy (increased risk of relapse) [3].

Measurement of disease activity and ophthalmological monitoring

A correct monitoring of the evolution of JIA-associated uveitis requires a close collaboration between the ophthalmologist and the pediatric rheumatologist, who will jointly decide if the evolution is favorable or if therapy escalation is required. Patients with JIA and controlled uveitis in whom topical corticosteroid or systemic therapy dosage/administration is decreased or stopped are at high risk of relapse even after long periods of remission. Ophthalmological monitoring will be performed at least every 2 months for at least 1 year after stopping therapy(afterwards, the monitoring will take place less frequently.) There are no precise recommendations for patients with chronic uncontrolled anterior uveitis [3].

Evolution of JIA-associated uveitis. Complications

The activity of uveitis may be independent of that of associated arthritis, so that uveitis may begin even during articular manifestation remission. The long-term evolution of CAU is variable (lasting from a few months to over 10 years), but in some cases the disease may continue into adulthood. In the light of the new therapies, the disease duration can be significantly shortened if initial uveitis is treated aggressively, as close as possible to the time of onset [8]. In 25-50% of the cases, uncontrolled CAU can lead to severe complications (synechiae, cataract, glaucoma) and in 10-20% of the cases, to blindness [3]. Due to the presence of symptoms, AAU is usually treated promptly, so that long-term sequelae are rare and the prognosis of this form is good. Complications with chronic visual disturbances (sometimes irreversible) can be secondary both to the progression of the uncontrolled disease (often found at the time of diagnosis) and to the treatment (e.g. long-term topical corticosteroid therapy). Structural complications include: cataract, glaucoma, band keratopathy, epiretinal membranes, macular edema, amblyopia, hypotonia, sequelae of pigmented keratic precipitates [2].

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