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Overview of Immunosuppressive Therapies for the Management of Severe and Chronic Pediatric Uveitis

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Abstract

Immunosuppressants are used for the management of severe pediatric uveitis cases when the prognosis for vision is poor, in cases of recurrent or chronic uveitis, to achieve corticosteroid sparing or in cases of corticosteroid resistance. Immunosuppressants used in children are anti-metabolites (methotrexate, azathioprine, mycophenolate mofetil), cyclosporine, tacrolimus, and biologics, including adalimumab, infliximab, anakinra, canakinumab, and tocilizumab. The mechanisms of action and indications of the various immunosuppressants used in pediatric uveitis are described in this overview.

Keywords: *pediatric uveitis, inflammation, mechanisms of action, indications, refractory, severe, chronic, immunosuppressive therapy, immunosuppressants, disease-modifying anti-rheumatic drugs, biologics, methotrexate, anti-TNF-alpha, azathioprine, cyclosporine, mycophenolate mofetil*

Introduction

Uveitis are rare in children, with a prevalence of approximately 30 per 100,000, and an incidence of 3-6 per 100,000 worldwide [1,2]. Children can present with severe and complicated forms of uveitis for multiple reasons. Clinical examination may be limited by the child's ability to cooperate and their age. Besides, several forms, especially that occurring in juvenile idiopathic arthritis (JIA), are usually asymptomatic for a long time and are diagnosed at a complicated stage, resulting in severe vision loss in 25-33% of pediatric uveitis cases [3]. Therapeutic care represents a real challenge. Some systemic treatments, such as corticosteroids, are more harmful in children, and can cause growth retardation, weight gain, and all of the known side effects of corticosteroids. Moreover, the side effects of topical corticosteroids or periocular injections such as cataracts and glaucoma may be more difficult to manage than in adults [4,5]. Therefore, the use of disease-modifying antirheumatic drugs (DMARDs) and biological agents plays a key role in the management of severe and refractory pediatric uveitis.

Immunosuppressive therapies are indicated in cases of severe impairment involving the prognosis for vision or life, in cases of recurrent or chronic uveitis, to achieve corticosteroid sparing or in cases of corticosteroid resistance or corticosteroid dependence. Corticosteroid dependence is defined as the need for a dose of corticosteroids greater than 10 mg per day of oral prednisone equivalent and 2 drops per eye per day of local dexamethasone for 6 cumulative months or 3 drops per day for 3 months in order to achieve and maintain disease control [6]. Because they are long-term treatments with possible toxicity, they require close collaboration between ophthalmologists and pediatricians to initiate the molecule and monitor its effectiveness and its side effects.

Immunosuppressants authorized in children and used in ophthalmology are DMARDs antimetabolites (methotrexate, azathioprine, mycophenolate mofetil), cyclosporine, tacrolimus, and biological agents infliximab, adalimumab, anakinra, canakinumab, and tocilizumab (Figure 1). Rituximab is not allowed in children. Alkylating agents are not used in ophthalmology because of their excessive toxicity, in particular their gonadal toxicity. Interferons and intravenous immunoglobulins are rarely used in pediatric ophthalmology.

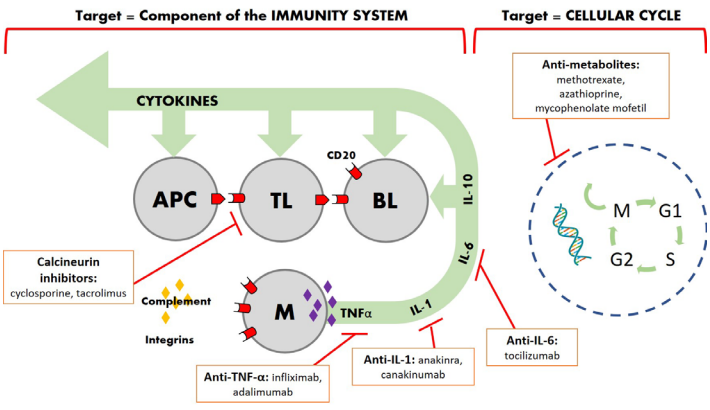

Figure 1: *Mechanisms of action of immunosuppressive therapies used in pediatric uveitis.*
APC: Antigen Presenting Cells, TL: T lymphocyte, BL: B lymphocyte, M: macrophage, IL: interleukin, TNF: Tumor Necrosis Factor. Cell cycle phases: M: Mitosis, S: Replication, G1 and G2 phases.

Mechanisms of action and indications for immunosuppressants

Methotrexate (MTX) is the most prescribed molecule in children in ophthalmology [7,8] and often prescribed as a first-line immunosuppressive drug. MTX works as an antimetabolite; it is a structural analogue of folic acid that inhibits by competition the dihydrofolate reductase necessary to de novo synthesis of purine bases (adenine and guanine) and of one pyrimidine base (thymine), mainly during the cell replication phase. It is indicated in JIA-related uveitis refractory to corticosteroids [9-11], and in uveitis not associated with JIA [12], in sarcoidosis [13], in uveitis associated with the HLA-B27 antigen, in Vogt-Koyanagi-Harada disease [14] and idiopathic intermediate uveitis and pars planitis [8]. Approximately 15% to 50% of children have refractory uveitis despite optimal treatment with methotrexate [9,10,15].

Azathioprine is a prodrug of 6-mercaptopurine. A complex cascade of reactions leads to the synthesis of different metabolites that inhibit the synthesis of purine bases and thus the proliferation of T lymphocytes (TL) mainly, but also of B lymphocytes (BL) and Natural Killer cells (NK). It is used in children in uveitis associated with Behçet's disease [13,16,17] and in idiopathic intermediate uveitis and pars planitis [18].

Mycophenolate mofetil inhibits inosine monophosphate dehydrogenase, an enzyme essential to de novo synthesis of purine bases. It is mainly active in T and B lymphocytes. There are few data in the literature in children. This agent is used in various indications including intermediate uveitis and pars planitis [12,19,20].

Anticalcineurins inhibit the production of interleukin-2 (IL-2). In a physiological situation, the recognition of the antigen by TL provokes a cascade of reactions, which results in the increase of intracellular calcium and the activation of calcineurin. Activated calcineurin dephosphorylates NFAT (Nuclear factor of activated T-cells) transcription factor which thus penetrates into the nucleus of the TL and allows IL-2 gene transcription. IL-2 will itself induce TL proliferation and cytokine production. Cyclosporine and tacrolimus bind to cyclophilin and FKBP-12 respectively, which inhibits calcineurin activation, NFAT translocation and therefore IL-2 transcription. Cyclosporine is particularly effective in pediatric uveitis in Behçet's disease [13,16,17] and is also used in intermediate uveitis and pars planitis [18,21]. However, it is now little used because of its toxicity (arterial hypertension, nephrotoxicity) and the arrival of recent therapies such as biologics. Tacrolimus is also rarely used in pediatric uveitis.

More recently, anti-tumor necrosis factor alpha (anti-TNF-alpha) biologics have proven to be effective in severe or chronic pediatric uveitis and are increasingly used in these indications, reducing the use of conventional immunosuppressants such as azathioprine, mycophenolate mofetil or cyclosporine [7,22-28]. The most widely used anti-TNF agents are adalimumab and infliximab. Anti-TNF-alpha inhibits TNF-alpha either by binding directly to it (-mab = monoclonal antibody) or by mimicking its receptor (-cept = receptor). TNF-alpha is a cytokine mainly produced by macrophages; its release is stimulated by antigenic danger signals present on the surface of bacteria and fungi membranes and tumor cells membranes. The release of TNF-alpha is also stimulated by several mediators, such as IL-1, IL-2 and interferon-γ. It has direct and indirect anti-inflammatory effects by stimulating the production of IL-1 and IL-6, by stimulating leukocytes phagocytosis and by increasing the adhesion capacities of inflammatory cells promoting the recruitment of immunity cell. Experimental models of autoimmune uveitis have demonstrated the central role of TNF-alpha in those inflammatory mechanisms [29]. Monoclonal antibodies are partially or fully humanized. They have a constant human constant region Fc and an antigenic recognition region Fab whose murine regions proportion is variable: partially murine and human for the oldest (infliximab), totally human for the most recent (adalimumab and golimumab). The nomenclature adopted by the World Health Organization takes into account the origin and target of the antibody. Thus, it can be a chimeric [-xi-mab], humanized [-zu-mab] or human [-u-mab] antibody. In the case of immunomodulators, the target is an interleukin [-ki(n)-X-mab] or another component of the immune system [-li(m)-X-mab]. By binding to TNF-alpha, monoclonal antibodies inhibit its effect and reduce inflammatory phenomena. They also cause the lysis of TNF-alpha-producing cells.

Adalimumab is the only US Food and Drug Administration (FDA) approved steroid-sparing agent for the treatment of pediatric uveitis, specifically for JIA-associated uveitis [30-32]. It has been used with success in pediatric Vogt-Koyanagi-Harada disease [14,33] and Behçet's disease [13,16,17]. Infliximab has also been used in Behçet's disease [13,16,17]. The induction of antibodies to anti-TNF-alpha agents, especially infliximab, is described and can lead to treatment failure. Recent meta-analysis by Maccora et al. showed the efficacy of adalimumab and infliximab in childhood chronic uveitis; adalimumab results were superior to those of infliximab [34]. Etanercept is a soluble receptor for TNF-α. It causes competitive inhibition of TNFα binding to cell surface receptors. It is now little used in the treatment of uveitis [35]. Several studies have indeed shown a lower efficacy compared to other anti-TNF-α (22,26,36,37) and some cases of possible etanercept-induced uveitis and scleritis have been described in adults [26,38-41].

Multiple other biologics targeting the interleukins have been used in severe and refractory pediatric uveitis. Tocilizumab (anti-IL-6) has been studied in severe JIA-associated uveitis refractory to anti-TNF-alpha and has shown its benefit, particularly in cases of cystoid macular edema [42-45]. In the APTITUDE Trial published in 2020, 21 patients aged 2-18 years with active JIA-associated uveitis treated with stable dose of methotrexate and refractory to anti-TNF-alpha received tocilizumab treatment; seven patients responded to treatment [43]. Finally, other biologics including sarilumab (anti-IL6), anakinra (anti-IL1), canakinumab (anti-IL-1β), gevokizumab (anti-IL-1β) and ustekinumab (anti-IL23 and anti-IL12), are being evaluated for the management of severe pediatric uveitis [46].

Therapeutic strategy

Treatment of the cause of uveitis is started when possible. Symptomatic treatment consists in a stepwise anti-inflammatory treatment, adapted to the anatomical form of the uveitis, its severity and the response to treatment. Topical corticosteroids are used as first-line treatment, as well as mydriatic and intraocular pressure-lowering eye drops to prevent and treat the complications of inflammation. Subconjunctival injections of betamethasone may be occasionally associated to topical corticosteroids in cases of severe anterior inflammation or macular oedema [47]. Other periocular injections are avoided in children. Systemic corticosteroids are used to control inflammation refractory to local and/ or regional treatment. Intravenous corticosteroids are sometimes needed when the inflammation is severe and sight-threatening, for example in case of posterior involvement such as Behçet's disease. Immunosuppressive therapies are the last

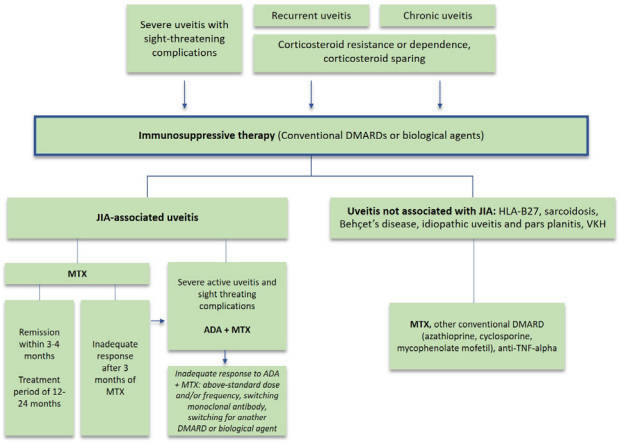

Figure 2: *Decision tree diagram for the use of immunosuppressive therapy in children with severe and chronic uveitis.*
DMARD(s): Disease-Modifying Antirheumatic Drug(s), JIA: Juvenile Idiopathic Arthritis, MTX: Methotrexate, ADA: Adalimumab, VKH: Vogt-Koyanagi-Harada Disease

step in managing pediatric uveitis. They are indicated in children with chronic inflammation refractory to local and/ or systemic corticosteroids to achieve steroid sparing, but can also be used during the acute phase in sight-threatening complicated cases. Given the side effects of corticosteroids in children and the frequent need for prolonged systemic treatment, the therapeutic escalation is more rapid than in adults and immunosuppressive therapy is initiated early in the disease course or even immediately.

In uveitis associated with juvenile idiopathic arthritis (JIA), the therapeutic strategy is firstly based on initial intensive topical corticosteroid therapy, then decreased according to the severity of the inflammation [48]. If local treatment fails, oral corticosteroid therapy can be useful in severe cases but immunosuppressive therapy is rapidly needed when there is a topical corticosteroid dependence or resistance or a sight-threatening complication. MTX is the most frequently used agent with a well-known safety and efficacy profile [9,49,50], allowing remission within 3-4 months and requiring a minimum treatment period of 12 months after remission, 24 months in the aggressive forms. Using subcutaneous methotrexate is recommended over oral methotrexate when starting systemic treatment for uveitis [35]. Anti-TNF-alpha agents are used in children with uveitis refractory to corticosteroids and conventional DMARDs and in children with severe active uveitis and sight-threatening uveitis [35]. As said above, adalimumab is the only FDA-approved non-steroid medication in pediatric uveitis and is approved for the management of JIA-associated uveitis. Several studies have shown its efficacy [24,30,51,52], in particular two double-blind randomized controlled trials against placebo, the SYCAMORE Study in 2017 [31,52] and the ADJUVITE Study in 2018 [30]. In the SYCAMORE Trial, 90 children (mean age 8.9 years) with active JIA-associated uveitis and taking a stable dose of methotrexate were assigned to receive either adalimumab or placebo. Treatment failures were observed in 27% of cases in the adalimumab group and in 60% of cases in the placebo group. In the ADJUVITE Study, 31 children (median age 9.5 years) with early onset JIA-associated or idiopathic anterior uveitis were assigned either to adalimumab or placebo. At month 2, there were 56% of responders on adalimumab and 20% on placebo. The use of adalimumab is recommended for children above the age of two and adolescents with chronic non-infectious anterior uveitis associated with JIA in case of insufficient response or intolerance to conventional treatment, in combination with MTX and corticosteroids. This molecule is used after 3 months of MTX failure. The most common side effects of adalimumab reported in the Strive Registry [53] are infections, injection site reactions and abnormal liver tests.

In HLA-B27-associated uveitis, systemic corticosteroids are used in case of resistance to local treatment for anterior uveitis, posterior involvement causing visual loss (macular edema, optic disc edema). Immunosuppression is indicated in cases of chronicity and to achieve corticosteroid sparing. It is used earlier than in adults. Corticosteroid therapy is often used to manage acute complications until the immunosuppressant is effective. As in adults, the most widely used immunosuppressant is MTX.

The indications for systemic corticosteroids in sarcoidosis are the same than the ones recommended in adults: failure of local treatment, macular edema, optic disc edema, extensive vasculitis. Immunosuppression is indicated in cases of corticosteroid dependence, corticosteroid resistance or poor tolerance. The most widely used molecule in children is MTX [13].

Several retrospective studies have been carried out in children with uveitis associated with Behçet's disease and describe the systemic treatments used [13,16,17]. Systemic corticosteroids, usually intravenous followed by oral therapy, associated with an immunosuppressant are recommended in case of posterior involvement. The immunosuppressants mostly used are cyclosporine, although this molecule is now little used, as well as azathioprine, and anti-TNF-alpha when the inflammation is severe. Interferon- α is used rarely.

The treatment of idiopathic intermediate uveitis and pars planitis is based on systemic corticosteroid therapy if the vision is threatened (dense vitritis, macular edema, optic disc edema, extensive vasculitis). Unlike adults, periocular injections of triamcinolone or intra-vitreous injections of dexamethasone are not performed because of the major risk of subcapsular cataracts and steroid-induced glaucoma. An immunosuppressant is necessary in case of chronicity, to achieve corticosteroid sparing, corticosteroid resistance or intolerance to corticosteroid therapy. The main agent used in children is methotrexate. The other molecules used are mycophenolate mofetil, azathioprine and cyclosporine [18,19,21].

Pediatric Vogt-Koyanagi-Harada disease is treated during the acute phase with high-dose intravenous corticosteroids followed by prolonged oral corticosteroids. Immunosuppressive therapy can be added to corticosteroids for the management of acute severe inflammation. It is also indicated in chronic forms in cases of corticosteroid resistance, corticosteroid dependence or recurrence, or in cases of poor tolerance to corticosteroids. The agents of choice are MTX and adalimumab [14,33].

Conclusion

Immunosuppressive therapies play a central role in the management of severe and chronic pediatric uveitis. They allow control of inflammation of uveitis that threaten vision or refractory to other therapies. These treatments require close and prolonged monitoring. Methotrexate is the most frequently used agent in children and has a well-known safety and efficacy profile, but biologics, especially adalimumab, are more and more showing their efficacy in these indications and taking an increasingly key place in the therapeutic strategy of these children.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest.

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