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USES OF METHOTREXATE IN OPHTHALMOLOGY: A REVIEW

Ophthalmology

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ABSTRACT

Methotrexate is a folic acid antagonist and immunosuppressive agent, which is being increasingly used in various ocular inflammatory diseases. Its use in ophthalmology has been increasing in recent years because of its anti-inflammatory activity and corticosteroid-sparing objective. It is currently used in recurrent anterior uveitis, intermediate uveitis, posterior or panuveitis, scleritis, peripheral ulcerative keratitis, necrotizing keratitis in rheumatoid arthritis, high-risk penetrating keratoplasty, etc. In addition to systemic administration of drug, intraocular administration of methotrexate can be a promising treatment option for uveitis. This article reviews the current trends and uses of methotrexate in ophthalmology and its related complications.

KEYWORDS:

methotrexate, immunosuppressive, uveitis, peripheral ulcerative keratitis.

Introduction

Methotrexate is categorized as an antimetabolite and has been used in the treatment of certain cancers since 1950s. It was approved by the United States Food and Drug Administration as a treatment for rheumatoid arthritis in 1988. It was formerly known as Amethopterin, a folic acid antagonist that competitively inhibits dihydrofolate reductase (DHFR), thereby blocking the formation of purines and pyrimidines within the cell, and consequently inhibiting DNA synthesis. Hence, it inhibits cell growth and proliferation by depleting the pool of reduced folates or tetrahydrofolates, induce T- cell apoptosis, modification of the B- cell response and cytokine production inhibition.[1]

Pharmacokinetics

Absorption of oral methotrexate is 30% on an average and is variable at high doses. Intramuscular and subcutaneous administration of methotrexate is completely absorbed. It is metabolized in liver to7-hydroxymethotrexate. Protein binding is 50%-60%. The half-life for low dose methotrexate (<30mg/m^2) is 3-10 hours and high dose methotrexate is 8-15 hours.

Role in ocular inflammatory diseases

Use of methotrexate as a treatment for ocular inflammation was first reported in 1965 by Wong and Hersh.[2] Although corticosteroids are still the mainstay of treatment for the management of non-infectious ocular inflammatory diseases, immunomodulatory agents including methotrexate are administered in addition to corticosteroids in patients refractory to corticosteroid treatment or to prevent steroid induced side effects.[3] Various indications of methotrexate are summarized in Table 1.

Table 1

1. Uveitis - non-specific - specific	Recurrent anterior uveitis, intermediate, posterior and panuveitis, childhood chronic uveitis
2. Scleritis	Behcet disease
3. Ocular membrane pemphigoid	Birdshot chorioretinopathy Sarcoidosis Multifocal choroiditis with panuveitis
4. Peripheral ulcerative keratitis	Vogt Koyanagi - Harada disease
5. High risk penetrating keratoplasty	Sympathetic ophthalmia

Similar to its administration in rheumatic diseases, methotrexate is administered intermittently at low doses (7.5-25mg/kg per week orally) with folic acid supplementation in ocular inflammation.[3] Parenteral administration via subcutaneous or intramuscular injections may increase the bioavailability and improve tolerance in patients with gastrointestinal disorders. It requires 6-8 weeks to be completely effective.[4]

Recurrent anterior uveitis

Acute anterior uveitis is the most common form of uveitis, and is frequently associated with the HLA-B27 haplotype and spondyloarthritis. It has been reported that 34% of patients with uveitis have acute anterior uveitis that recurs in either a variable period of time or after completion of topical corticosteroid taper.[5] Methotrexate was successfully used by Munaz-Fernandez et al[6] in a prospective study that showed after starting methotrexate treatment in patients with 2-3 episodes in the previous year, the number of recurrences is significantly reduced. The patients were started at a dose of 7.5 mg per week with folic acid. When a flare-up occurred, the dose was increased by 5 mg per week to a maximum of 20 mg.

Chronic non-infectious uveitis

Samson et al[7] retrospectively evaluated use of methotrexate in 160 patients, defining success as presence of < 1+ cellular reaction for 6 months or the absence of active lesions in posterior uveitis cases, they achieved control of inflammation in 76% patients and were able to taper prednisone to ≤ 8 mg/d in 64% of their patients. SITE Cohort Study by Gangaputra et al[8] in 384 patients suggested that adding methotrexate to an anti-inflammatory regimen is moderately effective for management of inflammatory activity and for achieving corticosteroid-sparing objectives.

Uveitis in children

Uveitis though relatively uncommon in children is a serious, potentially blinding disease. Juvenile idiopathic arthritis (JIA) is the most common cause followed by idiopathic uveitis and pars planitis.[9,10] Weiss et al[11] described the use of low dose subcutaneous methotrexate in 7 chidren with JIA associated uveitis. All patients had chronic active uveitis for at least 1 year inadequately suppressed with corticosteroids. The use of methotrexate decreased the severity of uveitis in six of seven patients and allowed for the discontinuation or reduction of corticosteroid.

Non –infectious scleritis

Methotrexate seems to be well-tolerated therapy that can reduce inflammation successfully and can decrease the corticosteroid requirement in treatment of chronic, non-infectious and non-

necrotizing scleritis. In a retrospective study conducted by Jachens et al[12] in 18 patients with non- necrotizing scleritis inflammation control was achieved in 10 patients and successful corticosteroid sparing was achieved in 10 patients.

Ocular cicatricial pemphigoid

Ocular cicatricial pemphigoid (OCP) is a chronic, progressive, cicatrizing inflammatory disease of presumed autoimmune etiology affecting the mucous membranes and skin. It has sight-threatening ocular manifestations such as chronic cicatricial conjunctivitis, progressive conjunctival fibrosis, and corneal epitheliopathy. Its response to immunosuppressive treatment is poorly known. Low dose weekly methotrexate is a useful first-line treatment for mild to moderate OCP.[13] McCluskey et al[14] in a retrospective study on 12 patients with OCP and 5 patients with drug-induced ocular cicatricial pemphigoid concluded that control of conjunctival inflammation was achieved and progression of cicatrization was prevented. Visual acuity was maintained or improved in 85% of total eyes treated with methotrexate monotherapy as the first line systemic agent.

Peripheral ulcerative keratitis (PUK)

Many studies have documented that patients with PUK who have associated systemic diseases have recurrences following localized temporizing treatment unless given adequate systemic immunosuppression therapy. To address the underlying problem, both systemic steroid and cytotoxic immunosuppressive medications have been used. Immunosuppressive agents have been indicated for management of following:

- PUK associated with potentially lethal systemic vasculitic syndromes such as PAN, Rheumatoid arthritis, SLE, Wegener's granulomatosis etc.
- PUK associated with necrotizing scleritis with vasculitis
- Bilateral and /or progressive Mooren ulcer
- PUK unresponsive to aggressive conventional medical and surgical therapy.

However, studies validating the efficacy of methotrexate in treatment of PUK are still lacking.

High-risk penetrating keratoplasty

The allograft rejection rate in high risk cases is in the range of 70% even with maximum local and systemic immunosuppression.[15] According to various literatures high-risk keratoplasties are recipient corneas with all quadrants of vascularization,[16] previous failed grafts, unstable ocular surface with repeated breakdown, prior inflamed eyes, post-chemical injuries, HSV keratitis, large adherent leucomas. There are case series of Methotrexate being used postoperatively in tectonic corneal grafts done for peripheral corneal melts and in high-risk penetrating keratoplasty.[17,18]

Adverse effects of systemic Methotrexate

Though an effective disease-modifying agent, the probability of discontinuation of methotrexate is 34% in 2 years in rheumatoid arthritis patients.[19] The major factor for discontinuation of methotrexate is probably due to folate antagonism or folate deficiency. Therefore folic acid supplementation is required to reduce the toxicity. The various studies on the safety of methotrexate for ocular inflammatory condition showed little risk of serious side effects during treatment enumerated in Table 2.

Table 2

Gastrointestinal distress
Bone marrow suppression
Increased level of liver enzymes
Malaise
Anorexia/nausea
Allergy
Mouth ulcers
Infections
Respiratory complaints
Hair loss
Cirrhosis

In a retrospective study by Gangaputra et al[8] methotrexate was discontinued because of the following side effects in 16% of 384 patients: gastrointestinal distress (2.9%), bone marrow suppression (2.6%), increased level of liver enzymes (2.3%), malaise (2.1%), allergy (1.6%), mouth ulcers (1.3%), infectious (0.8%), respiratory complaints (0.5%), hair loss (0.5%), liver cirrhosis (0.3%) and others (1.8%). Therefore, complete blood count and liver function tests should be conducted at every 4-6 weeks interval to monitor any serious adverse effect.

Methotrexate is a known teratogen, even at doses of 10mg/week, with the critical period being 8 and 12 weeks postconception, exposure during this period can cause miscarriages and fetal malformations.[20]

Newer horizon- Intravitreal methotrexate

Taylor et al[21] in a prospective study on 15 patients with unilateral exacerbation of noninfectious intermediate, posterior uveitis or panuveitis and/or CME with a history of increased intraocular pressure in response to corticosteroid administration injected intravitreal methotrexate at a dose of 400μg in 0.1 ml, improvement in visual acuity and reduction in CME was seen. Though relapse at 4 months was seen in some patients, but reinjection had similar efficacy.

Conclusion

Systemic administration of low doses of methotrexate is moderately effective in suppressing inflammation and in decreasing the dose of corticosteroids in patients with nearly all types of ocular inflammatory conditions. Methotrexate is usually well tolerated by most patients, with little serious side effects. However randomized control trials are needed to more accurately determine the safety of higher doses and/or subcutaneous administration to improve a patient's treatment success with methotrexate. Intravitreal administration can be a promising route of administration for patients who are vulnerable to systemic immunosuppressive therapy.

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