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ROLE OF METHOTREXATE IN THE MANAGEMENT OF NON- INFECTIOUS OCULAR AND ORBITAL INFLAMMATION: A PROSPECTIVE STUDY

Ophthalmology

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ABSTRACT

AIM To evaluate the clinical usefulness of methotrexate in patients with non-infectious ocular and orbital inflammatory disease who fail to respond to systemic corticosteroids

METHODS One year prospective study involving patients with non-infectious ocular and orbital inflammatory disease who were treated with methotrexate at a tertiary health care centre from march 2017 to February 2018.. Methotrexate was administered at a median maximum dose of 20 mg per week (range 15–25 mg per week) in conjunction with folate supplementation. Patients were followed with regular ophthalmic examinations, as well as serum liver enzyme levels and blood cell counts. Clinical signs of regression of the ocular and orbital inflammation, visual acuity, dosage and duration of methotrexate therapy, requirement for concurrent corticosteroid administration, and adverse drug reactions were recorded.

RESULTS Among 64 patients (112 eyes) observed from the point of addition of methotrexate to an anti-inflammatory regimen, 39.28%, 12.5%, 21.4%, 1.7%, 17.85%, and 7.14%, respectively, had anterior uveitis, posterior or panuveitis, scleritis, ocular mucous membrane pemphigoid, and thyroid orbitopathy and non specific orbital inflammation. In these groups, complete suppression of inflammation sustained for ≥28 days was achieved within 6 months in 63.6%, 21.42%, 29.1%, 0%, 60%, and 37.5%, respectively. Corticosteroid-sparing success (sustained suppression of inflammation with prednisone ≤10 mg/d) was achieved within 6 months among 56.8%, 21.42%, 25%, 100%, 55%, and 37.5%, respectively. Overall, success within 12 months was 66% and 58.4% for sustained control and corticosteroid sparing ≤10 mg), respectively.

CONCLUSION Methotrexate is a well tolerated immunosuppressive medication which may benefit patients with recalcitrant non-infectious ocular and orbital inflammatory disease.

KEYWORDS

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]

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]

PATIENTS AND METHODS

We examined 64patients (112 eyes) with non-infectious ocular and orbital inflammatory disease treated consecutively at a tertiary health care centre from march 2017 to February 2018.. The institutional review board gave approval for this study.

Patients with alcoholism or known liver disease were excluded. The initial dose of methotrexate was 7.5 mg per week orally, increased to 15 mg per week, 1 week later. The dose was increased at monthly intervals to a maximum of 25 mg per week depending on clinical response and side effects. We routinely prescribed folate supplements in a dose of 1 mg per day orally, and counselled against alcohol consumption with monthly follow up.. We would generally obtain baseline serum creatinine level and liver function tests, a full blood cell count and viral hepatitis B and C serology before beginning treatment. Liver function tests and blood cell count were then monitored 2–4 weeks after every dosage change, and every 2 months for a stable dosage. The alternative to taper and discontinue methotrexate was always discussed with patients who had been in clinical remission for 6–12 months. This decision was ultimately based on patient preference, as guided by physician judgment.

We studied demographic details, aetiological diagnosis, previous therapies, indication for commencing methotrexate, dosage schedule, duration of treatment, reason for ceasing methotrexate, concurrent corticosteroid usage, clinical response to treatment, adverse drug reactions, and length of follow up.

Inflammatory status was categorized as “active,” “slightly active,” or “inactive” for every eye at every visit, based on the clinician's notations at the time of each visit. The study defined “slightly active” inflammation as “activity that is minimally present, described also by terms such as mild, few, or trace cells, and so on,” whereas inflammation was scored as inactive when described by terms such as “quiet,” “quiescent,” “no cells,” and “no active inflammation.” Anterior chamber cells had been graded at the time of clinical examinations in a manner generally similar to the system ultimately adopted for this purpose by the Standardization of Uveitis Nomenclature Working Group.[4]Vitreous cells had been graded on an ordinal scale of 0, 0.5+, 1+, 2+, 3+, and 4+. Vitreous haze, when available, was graded according to the National Eye Institute system,[5] subsequently adopted by the Standardization of Uveitis Nomenclature Working Group,[4] or a post hoc approximation thereof. Corticosteroid-sparing effects were evaluated based on time to reduction of the prednisone dose to 10, 5, or 0 mg without reactivation of the ocular inflammation, among those not meeting the respective criterion for success at the outset. Prednisone-equivalent doses of alternative corticosteroids[6] were calculated for these evaluations when necessary. Objective criteria for clinical benefit in orbital inflammation included relief of pain and diplopia, reduction of proptosis and lid oedema, improved ocular motility, and resolution of conjunctival injection and chemosis.

Pretreatment and post-treatment visual acuities were also recorded

Statistical Methods

Frequencies of variables at enrollment and outcomes were tabulated for the study population using SPSS Version 22.0. Outcomes were not accepted until they had been observed over ≥2 visits spanning ≥28 days, to avoid counting transient improvements and brief interruptions of therapy as successes or failures.

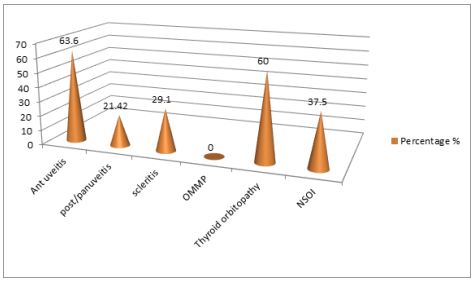
RESULTS

64 patients (112 eyes) used methotrexate as the only treatment for ocular and orbital inflammation other than local therapies, corticosteroids, and nonsteroidal anti-inflammatory drugs. These patients were followed up at the center while taking methotrexate monotherapy for 12 months. The characteristics of the patients and their involved eyes at the time of starting methotrexate are given as Table 1. The median age was 46.9 years. There were predominantly female(72.9%). A total of 112 eyes were affected by different forms of ocular and orbital inflammation, including anterior uveitis (24patients; 44 eyes), posterior uveitis or panuveitis (12 patients; 14 eyes), scleritis (14 patients; 24 eyes), ocular mucous membrane pemphigoid (1patient; 2 eyes) and Thyroid orbitopathy (10 patients; 20 eyes)and non specific orbital inflammation (5 patients; 8 eyes) . At the time of starting methotrexate, 73.43% of patients had bilateral involvement, 32 eyes (35.84%) had a visual acuity of ≤20/50, and 46 eyes (41.07%) had slightly active or active inflammation.

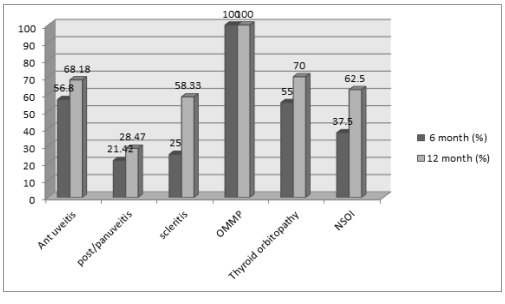
Table 1.

Characteristics	Anterior uveitis	Post/ panuveitis	Scleritis	Ommp	Thyroid orbitopathy	Non sp orbital inflammatio
Patients no.	24	10	14	1	10	5
No. of eyes	44	14	24	2	20	8
Median age	33.9	44.0	46.4	52.5	42.0	38.2
Bilaterality%	31.25	6.25	15.62	1.56	12.5	4.68
Unilaterality%	6.25	9.37	6.25	0	3.12	3.12

In these groups, complete suppression of inflammation sustained for ≥28 days was achieved within 6 months in 63.6%, 21.42%, 29.1%, 0%, 60%, and 37.5%, respectively.



Corticosteroid-sparing success—defined as completely inactive inflammation at ≥2 visits spanning ≥28 days after tapering the prednisone dose to ≤10 mg/d—was achieved at or before 6 months among 56.8% of patients with anterior uveitis, 21.42% with posterior uveitis or panuveitis, 25% with scleritis, and 100% with ocular mucous membrane pemphigoid, 55% with thyroid orbitopathy and 37.5% with non specific orbital inflammation. Corticosteroid-sparing success also continued to improve with time, and was achieved at or before 12 months of methotrexate by 68.8% of patients with anterior uveitis, 28.47% with posterior uveitis or panuveitis, 58.33% with scleritis, and 100% with ocular mucous membrane pemphigoid, 70% with thyroid orbitopathy and 62.5% with non specific orbital inflammation.



In this study, deterioration of visual acuity was never the primary indication for treatment. No eyes showed significant reduction (2 or more Snellen lines) in visual acuity, and there was significant improvement of visual acuity in six of 24 treated eyes. 48 patients (75%%) experienced one or more side effects. 31 patients (48.4%) experienced fatigue, and the same number complained of various types of gastrointestinal disturbance. Other side effects included headache in six patients (9.3%), arthralgia in five patients (7.8%), and hair thinning in 8 patients (12.5%). Serum liver enzyme elevation was noted in 16 patients (25%), but these changes normalised either spontaneously or in response to a dose reduction.

DISCUSSION

Our results indicate that methotrexate is reasonably effective for ocular inflammation. However, not all patients experience treatment success, and several months of treatment may be needed before success is observed.

A number of non-comparative case series indicate that methotrexate may be useful in the management of various forms of uveitis, scleritis, and peripheral ulcerative keratitis[7-14] However, only one report has addressed the role of this medication for non-infectious orbital inflammatory disease. Shah and colleagues reported on methotrexate therapy for ocular inflammatory disease.[9]

In summary, our data suggest that when a patient with ocular inflammation meets indications for the addition of immunosuppressive therapy to a treatment regimen, addition of methotrexate has a moderate chance of achieving control of inflammation and/or of maintaining control of inflammation while tapering prednisone dosages to ≤10 mg. The beneficial effects of methotrexate may not be seen for months, during which time other therapies (typically corticosteroids) usually are needed to control inflammation. Methotrexate is likely to be well tolerated, and important long-term adverse effects seem to be rare when methotrexate is used and monitored in a manner similar to commonly accepted guidelines.[15] When side effects do occur, they are likely to be reversible. It would be valuable to identify biological or genetic markers predictive of a favorable response to methotrexate, which would enable methotrexate to be targeted to the patients most likely to respond to such therapy. The site of ocular inflammation may be one such factor, in that posterior and panuveitis seem less likely to respond to methotrexate than other forms of ocular inflammation, although this may reflect disease severity rather than differential responsiveness. Randomized, controlled trials would be valuable to determine more accurately whether use of higher doses and/or subcutaneous administration improve a patient's chances of treatment success with methotrexate.

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.

Footnotes

No conflict of interest

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