Subconjunctival methotrexate in the treatment of non infectious ocular inflammatory diseases

Metotrexate subconjuntival no tratamento de doenças inflamatórias oculares não infecciosas

Seiji Hayashi [1]
Rubens Belfort Jr [2]

SUMMARY

We studied the effect of subconjunctival injections of methotrexate (MTX) in 18 patients with non-infectious ocular inflammatory processes (unilateral anterior uveitis 11 patients, corneal graft rejection 3 patients, nodular sclerouveitis with no systemic disease 2 patients, Vogt-Koyanagi-Harada's disease 1 patient, and Behcet's disease 1 patient). Weekly subconjunctival injections of 7.5mg of MTX were given. Daily slit lamp examination was performed to evaluate the degree of inflammatory activity in the anterior chamber or sclera and conjunctiva during the treatment. Patients were clinically followed for an average of 7.8 months (3 to 12 months) and no patient had evidence of local or systemic side effects. The conjunctiva remained yellowish and edematous for approximately 24hs after the injections and returned to the previous aspect after that. Our results showed that subconjunctival weekly injections of low dose MTX have a favorable response in the treatment in nine of 11 cases of anterior uveitis, three cases of corneal graft rejection, and one patient of Vogt-Koyanagi-Harada disease. One patient with Behcet disease, and two with scleritis did not respond to the treatment.

Key-Words: Methotrexate; Eye; Uveitis; Inflammation; Immunosuppression; Drug

INTRODUCTION

Methotrexate (MTX) is a cytotoxic immunosupressive drug, analog of the folic acid, that acts by inhibiting dihydrofolate reductase, an enzyme necessary to convert folic acid to reduced folate cofactors. The inhibition of this enzyme results in depletion of folates necessary for both thymidylate and purine synthesis; thus formation of DNA is blocked and as a consequence the cellular synthesis is inhibited [1]. Hepatic and renal toxicity, pneumonitis and toxic reactions such as nausea, vomiting, mucositis and leukopenia are the most frequent adverse effects observed. These problems are usually related to the long term use of a high dose of the medication and it can be managed through appropriate reduction of the drug [2-4].

The use of systemic methotrexate in the treatment of autoimmune ocular diseases, such as sympathetic ophthalmia and chronic cyclitis, has been reported, and systemic dose of 25mg/m^2 of body surface area has shown good results [5-7]. Local MTX, in low dose (10mg), for intra-articular injection for the treatment of rheumatoid and psoriatic arthropaties as well as the use of low dose of systemic MTX in ophthalmology have been reported with good results [8-10].

This pilot study was performed to evaluate whether periocular injections of MTX is a suitable treatment of non infectious ocular inflammatory disor-

[1] Mestre em Imunologia, Dr. em Oftalmologia - Universidade Federal de SP - EPM - Setor de Córnea e Doenças Externas Escola Paulista de Medicina.
[2] Professor Tilular e Chefe do Departamento de Oftalmologia, Instituto da Visão da UNIFESP-EPM

Reprints to: Seiji Hayashi, MD - Departament of Ophthalmology - Paulista School of Medicine - UNIFESP - Rua Botucatu, 822 - CEP 04023 - São Paulo - SP - Brazil
email: seiji@pop-gw.mandic.com.br

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ders and also to evaluate its possible local and systemic side effects.

MATERIAL AND METHODS

Eighteen patients with non infectious ocular disease were studied at the Uveitis Section of the Department of Ophthalmology of the Escola Paulista de Medicina.

The patient selection was based on the clinical history, the ophthalmologic examination and a laboratorial work up that included the hematological profile and renal and hepatic functions, which were repeated every two weeks throughout the treatment period. Patients were previously treated with steroids for one week and the ones that did not respond or had a contraindication for the use of corticosteroids were included in the study.

No patient had any clinical or laboratorial evidence of systemic infection.

Methotrexate aqueous solution (25mg/ml concentration) was injected in a dose of 7.5mg/week in the superior subconjunctival region of the affected eye. Daily slit lamp examination was performed until day three after the injection to evaluate the degree of inflammatory activity in the anterior chamber and also the conjunctival aspect after the injection. The patient was reexamined after seven days, and if there was no sign of improvement he received another injection of MTX, and the same routine was applied in the following weeks. The patient was switched on to systemic immunesupression if the inflammation was worse. Inflammatory activity was graded in a score of O to 4 according to the number of inflammatory cells in the anterior chamber and the presence of flare as described previously in the cases of uveitis [11].

RESULTS

Eighteen patients were treated with subconjunctival injections of MTX (13 males and 5 females). The mean age was 38.6 years (range: 15-58 years). Thirteen were white (72%) and 5 were non white (28%). The average follow up period was 7.8 months (range from 3 to 12 months).

Non granulomatous anterior acute uveitis not associated with systemic disease represented 61.1% (11 patients) of our cases, the inflammation affecting one eye in all of them, the total number of injections was 22, with an average of 2.2 per patient (range: 1 to 4 per week), five patients showed a complete remission of the inflammatory picture, four presented a reduction of inflammatory cells and flare in the anterior chamber, and two did not improve.

Three patients with corneal graft rejection (16.8%) presented a remission of the anterior chamber reaction and decrease in the number and size of KPs after an average of 1.6 injections of methotrexate (range: 1-2 injections). Two patients with nodular scleritis not associated to systemic disease (11.1%) related a change for the worse after 1 injection. One patient with Vogt-Koyanagi-Harada's disease with granulomatous iridocyclites and no systemic manifestation (5.5%) presented remission of the inflammation after 5 injections. And 1 patient with Behcet's disease with retinitis and anterior chamber reaction (5.5%) presented only a decrease of the inflammation in the anterior chamber after 1 injection.

The conjunctiva remained yellowish and edematous for approximately 24hs after the injections and returned to the previous aspect after that. None of the patients presented any side effect related to the use of MTX.

DISCUSSION

We have observed that subconjunctival injections of MTX was effective in reducing the anterior chamber inflammation in uveitis and corneal graft rejection. To our knowledge this is the first report in the literature about subconjunctival injection of MTX for the treatment of non infectious ocular inflammation. The selection of MTX in the present study was justified to the following considerations: low toxicity when used in non-neoplastic disease, well understood pharmacological action, antiinflammatory properties, quite rapid onset of effect when compared to many of other agents, and capability to induce suppression of the mononuclear cells response [12]. And finally, the necessity for a new therapeutic approach suggested by the adverse effects from the chronic use of systemic and topical steroids in the treatment of ocular inflammation.

Low-dose MTX has been used for the treatment of non infectious uveitis. In these studies an oral dose from 7.5 to 15mg/week was used to treat patients and most of them responded satisfactory to the treatment with reduction of the inflammatory activity in the eye and few systemic side effects [9, 10].

In our study subconjunctival injections of MTX were given in a pulse form, once a week, in a dose of 7.5 mg. This route was chosen in attempt to have a maximal intraocular concentration of medication associated to the minimal systemic side effect. Some authors reported ocular irritation in patients using high-dose MTX to treat malignancy, they correlated symptoms like burning and pluritus to the presence of the drug in the tears [13]. In our study, although the medication was injected subconjunctivally, none of the patients presented any ocular side effect.

The mechanism of action of MTX as an anti-inflammatory drug is still not well understood. Recent studies show that administration of low dose MTX is associated with an increase in the concentration of the anti-inflammatory autocoid adenosine at the sites of inflammation, which results in decrease of leukocyte accumulation at

the inflamed areas [14]. Other studies show that low dose MTX inhibits leukotriene B4 and complement C5a induced neutrophil migration into the sites of inflammation [15]. We believe the local injection of MTX will promote this effects in the anterior chamber faster than given systemically.

Our results have shown, despite of the limitations of no appropriate controls, promising results in the treatment of ocular inflammatory process with low doses of weekly subconjunctival injections of this anti-neoplastic drug. Further controlled studies are needed to confirm our impression that this treatment is safe, simple and relatively effective in the treatment of non infectious ocular inflammation.

RESUMO

Estudou-se o efeito do metotrexate aplicado na forma de injeções subconjuntivais em 18 pacientes com processo inflamatório ocular não infeccioso (11 pacientes com uveíte anterior, 3 pacientes com rejeição de transplante de córnea, 2 pacientes com esclerouveíte nodular anterior não associado a doença sistêmica, 1 paciente com síndrome de Vogt-Koyanagi-Harada e 1 paciente com síndrome de Behcet). As injeções de metotrexate foram aplicadas na dose de 7,5mg e os pacientes foram examinados diariamente por biomicroscopia para avaliar o grau de inflamação na câmara anterior, esclera e conjuntiva durante o tratamento e seguidos por uma média de 7,8 meses (3 a 12 meses). Nenhum paciente apresentou qualquer evidência de efeito colateral local ou sistêmico. A conjuntiva apresentou-se amarelada e edematosa por 24 horas após a injeção, voltando ao aspecto prévio após esse período. Os resultados mostram que injeções subconjutivais de metotrexate apresentam resposta favorável no tratamento de nove dos 11 casos de uveíte anterior, três casos de rejeição de transplante de córnea e um caso de síndrome de Vogt-Koyanagi-Harada. Um paciente com síndrome de Behcet e dois pacientes com esclerite não responderam a medicação.

Palavras-chave: *Metotrexate; Olho; Uveíte; Inflamação; Imunossupressão; Drogas*

REFERENCES

1. HRYNIUK, W. M.; BROX, L. M.; HENDERSON, J. F.; TAMAOKI, T. - Consequence of methotrexate inhibition of purine biosynthesis in L5178 cells. *Cancer Res.*, **35**:1247, 1975.
2. DECKER, J. L. - Toxicity of immunosupressive drugs in man. *Arthritis Rheum.*, **16**: 89-91, 1973.
3. ROENIGK, H. H.; BERGFELD, W. F.; ST. JAQUES, R. - Hepatotoxicity of methotrexate. *Arch Dermatol.* **103**: 250-261, 1971.
4. STEINBERG, P. S.; and WINOKUR, S. H. - Immunosupressive and cytotoxic chemotherapy: long term complications. *Ann Inter Med.*, **82**: 84-95, 1975.
5. WONG, V. G. and HERSH, E. M. - Methotrexate in the therapy of cyclitis. *Trans Am Acad Ophthalmol Otolaryngol.*, **69**: 279-293, 1965.
6. WONG, W. V. - Methotrexate treatment of uveal disease. *Am J Med Sci.*, **251**: 239-244, 1966.
7. LOTTENBERG, C. L.; BELFORT JR, R.; ABREU, M. T.; DOMINGUES NETO, S.; HIRATA, P.S.; PETRILLI, A. M.N.; SILVA, M. H.; MULLER, M. E. W.; FARAH, M. E.; PLUT, R. C. A.; KIM, M.; REHDER, J. R. C. L.; BURNIER, M. N. - Seis pacientes com oftalmia simpática: experiência de 13 anos. *Arq bras oftalmol.*, **49**: 82-5, 1986.
8. HALL, G. H.; JONES, B. J. M.; HEAD, A. C.; JONES, V. E. - Intra-articular methotrexate - Clinical and laboratory study in rheumatoid and psoriatic arthritis. *Ann Rheum Dis.*, **37**: 351-356, 1978.
9. SHAH, S. S.; LOWDER, C. Y.; SCHMITT, M. A.; WILKE, W. S.; KOSMORSKY, G. S.; MEISLER, D. M. - Low-dose methotrexate therapy for ocular inflammatory disease. *Ophthalmol.*, **99**:1419-1423, 1992.
10. HOLZ, F. G.; KRASTEL, H.; BREITBART, A.; SCHWARZ-EYWILL, M.; PEZZUTTO, A.; VÖLCKER, H. E. - Low-dose methotrexate treatment in noninfectious uveitis resistant to corticosteroids. *German J Ophthalmol.* **1**:142-144, 1992.
11. NUSSENBLATT, R. B. and PALESTINE, A. G. - Examination of ocular structures. In Nussenblatt, R. B. and Palestine, A. G. (ed.): *Fundamentais and clinical practice,* Chicago, Year Book Medical Publishers, Inc., 1989, pp. 59-79.
12. CRONSTEIN, B. N. - Molecular mechanism of methotrexate action in inflammation. *Inflammation.* **16**: 411-423, 1992.
13. DOROSHOW, J. H.; LOCKER, G. Y.; GAASTERLAND, D. E.; HUBBARD, S. P.; YOUNG, R. C.; MYERS, C. E. - Ocular irritation from high-dose methotrexate therapy: pharmacokinetics of drug in the tear film. *Cancer.* **48**: 2158-2162, 1981.
14. CRONSTEIN, B. N.; NAIME, D.; OSTAD, E. - The antiiflammatory mechanism of methotrexate - Increased adenosine release at inflamed sites diminishes leukocyte accumulation in an in vivo model of inflammation. *J Clin Invest.* **92:** 2675-2682, 1993.
15. SUAREZ, C. R.; PICKETT, W. C.; BELL, D. H.; McCLINTOCK, D. K.; ORONSKY, A. L.; KERWAR, S. S. - Effiect of low dose methotrexate on neutrophil chemotaxis induced by leukotriene B4 and complement C5a. *J Rheumatol.*, **14:** 9-11, 1987.