

Review of Milestone Articles relating to Safety of Low Dose Methotrexate over the Years

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Toxicity of low dose Methotrexate in Rheumatoid Arthritis

Michael Weinblatt, Journal of rheumatology, 1985

Summary: Review of 587 patients found following side effects:

Gastrointestinal (GI) toxicity – 10% reported anorexia, nausea, vomiting, diarrhea, 2.5 % stopped drug due to these side effects and the others had mild cases, doses >25 mg/week were more toxic to GI tract with stomatitis reported in 6% and occurred within 1-5 days after drug administration

Skin – Side effects may develop in low doses with most common reactions:

hyperpigmentation, urticaria, and reactivation of ultraviolet light induced erythema

Alopecia has been reported, thinning of hair occurred in 1% of the cases in this review

Renal – rare in low doses used in rheumatoid arthritis

Hematologic – 3% developed a reaction in this review: leucopenia(low white blood cell count) was most common, anemia and thrombocytopenia less common

Reproductive: Male – has little and no lasting effect on slowly dividing spermatogonial stem cell population. Men previously treated with high doses have produced normal offspring.

Reproductive: Female – Two studies showed no effect on fertility or ovarian function and no congenital defects noted in women previously treated with high doses

Teratogenesis – birth defects noted if administered early in pregnancy

Malignancy – No evidence noted that it causes cancer

Pulmonary – hypersensitivity reaction has been noted with symptoms of cough, fever, and dyspnea

Miscellaneous toxicity – headache, dizziness shortly after drug administration and resolve in a few days

A Review of Clinical Applications and Side Effects of Methotrexate in Ophthalmology: A Review Article published 2020

This review article (Reference 2) aimed to highlight emerging clinical applications of MTX and examine its side effects, providing useful guidance for ophthalmology practitioners in clinical settings.

Summary: Numerous studies had been conducted to prove that MTX could be used as a well-tolerated, safe, and effective first-line treatment. Hence, the MTX administration should not continue to be stigmatized as a “cancer drug,” or to be discouraged because of associated adverse effects. Contrarily, the indication and the routes of administration are about to gradually widen.

Methotrexate for Ocular Inflammatory Diseases published 2009

This article (Reference 3) evaluated the outcome of treatment with methotrexate for noninfectious ocular inflammation in a retrospective cohort of 384 patients (639 eyes). This study concluded that adding methotrexate to an anti-inflammatory regimen not involving other nonsteroidal immunosuppressive drugs is moderately effective for management of inflammatory activity and for achieving corticosteroid-sparing objectives, although many months may be required for therapeutic success. Methotrexate was well tolerated by most patients and seems to convey little risk of serious side effects during treatment.

Low-dose Methotrexate Therapy for Ocular Inflammatory Disease published 1992

This is the abstract of Reference 4:

Background: Methotrexate is a second-line anti-inflammatory agent used in the treatment of rheumatic diseases. At low doses (12.5 mg/week), it is associated with few serious side effects.

Methods: Twenty-two patients (5 men, 17 women) with chronic noninfectious ocular inflammatory disease, who had not responded to or who had become intolerant of corticosteroid or alternate cytotoxic agents, were treated weekly with oral low-dose, pulse methotrexate. Treated diseases included chronic uveitis-vitreitis (9), scleritis (4), inflammatory pseudotumor (3), orbital myositis (3), and retinal vasculitis (3).

Results: Follow-up ranged from 2 to 39 months (mean, 11 months). Response time ranged from 3 to 9 weeks (mean, 5 weeks) after implementation of methotrexate therapy. Sixteen of 22 patients had reduction of inflammatory activity. Fourteen of these 16 patients were able to taper or discontinue corticosteroid therapy. Five patients had complete remission of their disease; six patients did not respond to methotrexate.

Conclusion: Treatment with low-dose methotrexate appears to be effective therapy for steroid-resistant ocular inflammatory disease.

References

- 1) Weinblatt ME. Toxicity of low dose methotrexate in rheumatoid arthritis. *J Rheumatol Suppl.* 1985;12 Suppl 12:35-9.
- 2) Ang G, Peng X. A Review of Clinical Applications and Side Effects of Methotrexate in Ophthalmology. *J Ophthalmol.* 2020;2020:1537689.
- 3) Gangaputra S, Newcomb CW, Liesegang TL, Kaçmaz RO, Jabs DA, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, Suhler EB, Thorne JE, Foster CS, Kempen JH; Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study. Methotrexate for ocular inflammatory diseases. *Ophthalmology.* 2009;116(11):2188-98.e1.
- 4) Shah SS, Lowder CY, Schmitt MA, Wilke WS, Kosmorsky GS, Meisler DM. Low-dose methotrexate therapy for ocular inflammatory disease. *Ophthalmology.* 1992 Sep;99(9):1419-23.