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Methotrexate as a Corticosteroid-Sparing Agent for Thyroid Eye Disease

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Abstract:

Objective: Thyroid eye disease (TED) is generally treated with oral corticosteroid therapy. A steroid sparing drug could be a useful adjunct. We reviewed our experience with methotrexate as a corticosteroid sparing agent to treat TED.

Methods: Retrospective chart review from two eye inflammation clinics. Patients with TED who were unable to discontinue prednisone therapy without disease recurrence were included.

Results: 14 patients who were receiving an average of 32 mg/day of prednisone were treated with methotrexate, usually 15 mg/week orally or 20 mg/week subcutaneously. Five patients discontinued therapy for a lack of benefit or intolerance. Of the 9 patients who remained on methotrexate, all were able to discontinue prednisone completely after an average duration of 7.5 months. Improved visual acuity by at least two lines on the Snellen chart was achieved by 7 of 12 patients with reduced acuity and partial improvement in ocular motility was achieved in 5 of 14 patients.

Conclusions: Methotrexate provided an effective steroid sparing effect in a subset of patients with TED.

Keywords: Graves' disease; Thyroid eye disease; Methotrexate; Corticosteroids; Prednisone; Immunosuppression

Introduction

Thyroid eye disease (TED) is an autoimmune disease associated mostly with Grave's disease. However, it can also be associated with Hashimoto's thyroiditis, thyroid carcinoma, primary hyperthyroidism, and primary hypothyroidism [1]. The common finding in TED that accounts for most of its clinical manifestations seems to be enlargement of orbital soft tissue and extra-ocular eye muscles [2]. Enlargement usually affects inferior and medial recti (75%), followed by superior and lateral recti (50%) [3]. TED can be distinguished from other orbital inflammatory diseases by its tendency to spare the tendinous portion of the extra ocular muscles. Histopathological studies of the TED orbit reveal an extensive deposition of hyaluronic acid (a hydrophilic glycosaminoglycan) between muscle fibers, a widespread inflammatory infiltrate, and an overabundance of cytokines [4,5]. The extensive deposition of hyaluronic acid in the periorbital fat creates an oncotic pressure difference and edema develops in the muscles and fat. Classic clinical symptoms of TED include proptosis, periorbital swelling, eye pain, impaired extra ocular motility, and visual impairment. The usual treatment for patients with TED is systemic corticosteroids such as prednisone. In some studies a higher efficacy with intravenous glucocorticoids over oral glucocorticoids for treating Graves' disease has been reported [6,7]. The chronic use of corticosteroids is associated with a wide variety of adverse effects including osteoporosis, infections, hyperlipidemia, diabetes mellitus, avascular necrosis, and cataract formation [8]. Because of such adverse effects from prolonged use of corticosteroids, steroid sparing agents such as rituximab [9] and methotrexate (MTX) have been used to treat patients with TED [10]. The goal of this study is to evaluate the efficacy of MTX as a steroid sparing drug for patients with TED.

Methods

This was a retrospective chart analysis of patients with thyroid eye disease who were treated with methotrexate as a steroid sparing agent at the Casey Eye Institute at Oregon Health & Sciences University or at the Legacy Devers Eye Clinic, Portland, Oregon. Permission to perform a retrospective chart review was approved by Oregon Health & Science University Institutional Review Board. Patients were treated between the years 1998-2014. A total of 21 patients were identified, 14 of whom were taking prednisone at the time that the methotrexate was initiated. This report focuses on those 14 patients receiving concomitant prednisone therapy with methotrexate since the reduction in prednisone dosage provided a quantifiable measure of effect. These 14 patients in this retrospective chart analysis had a previous history of corticosteroid dependence. The lowest average dose of corticosteroids that these patients tolerated without worsening of their ocular symptoms was 20 mg/day. Patients were administered either oral or subcutaneous doses of MTX or oral doses of prednisone. Average MTX oral dose was 15 mg/week and the average subcutaneous dose was 20 mg/week. Dosages were always administered once a week and a daily supplement of 1 mg of folic acid

was given to every patient. Both the Legacy Devers clinic and the Casey Eye Institute clinic are tertiary referral clinics. Both clinics accept patients with a variety of inflammatory eye diseases often treated with immunosuppression. Examples include uveitis, scleritis, orbital inflammatory disease, and mucous membrane pemphigoid. The majority of patients in this report were referred by orbital specialists after failing to respond adequately or to tolerate oral corticosteroids. Methotrexate is ordinarily the first corticosteroid sparing drug tried by the authors. Exceptions would include patients whose baseline serum liver enzymes are elevated and patients who are unwilling to moderate their alcohol intake.

During the course of the treatment, patients were followed at 1, 3, 6 and 12 months after starting treatment with MTX. Routine laboratory monitoring of the complete blood count and liver enzymes was requested every two months. If patients were found to have elevated liver enzymes or could not tolerate the MTX, dosage was adjusted or the medication was discontinued. All of the exophthalmometry values were taken utilizing a Hertel exophthalmometer and the normal value range used for this trial was of 12-21 mm. An improvement in proptosis required a reduction in the exophthalmometer reading by more than 2 mm.

Results

Fourteen patients who had been diagnosed with TED were started on methotrexate therapy either while receiving prednisone therapy or in five instances, at a time when when prednisone therapy was recommenced. There were 10 females (71%) and 4 males (29%) with a median age of 60. Eleven patients had Graves' disease, 1 hypothyroidism, 1 hypothyroidism/hyperthyroidism, 1 euthyroid with typical TED imaging showing bilateral extraocular muscle involvement.

The prednisone dose at the time of initiating methotrexate ranged from 5 mg to 80 mg with an average of 32 mg/day. Corticosteroid was taken orally. Patients had been receiving prednisone for a mean continuous duration of 2 months with a range of 0 to 5.5 months. Five patients, who began prednisone and methotrexate concomitantly, had taken prednisone previously, benefited from it, but tolerated it poorly. Prednisone was restarted as a "bridge" therapy since methotrexate has a slower onset of action compared to prednisone. The dose for restarting prednisone was generally lower than any prior prednisone trial due to the history of adverse effects. After MTX treatment, 9 out of 14 patients (64%) were able to taper their corticosteroid dosage to 0 mg. Information on the nine patients discontinuing prednisone is given in Table 1. The average time it took for patients to be able to discontinue corticosteroids was 7.5 months after starting MTX treatment. Five patients (35%) were not able to taper corticosteroids completely. Two of them switched to mycophenolate mofetil at an average of 2.5 months after starting MTX and 3 had to stop MTX treatment due to intolerance at an average of 4 months after starting MTX. Of the 3 patients who stopped MTX treatment: 1 stopped due to elevated liver function test (LFTs), 1 stopped due to a methicillin-resistant Staphylococcus aureus infection and 1 did not tolerate MTX due to severe muscle weakness and fatigue.

Methotrexate was given either orally or subcutaneously. Seven patients (50%) started on a subcutaneous dose, 7 patients (50%) started on an oral dose. The route of therapy was chosen primarily on patient preference and was sometimes changed after the initial dose. The average doses were 20 mg/week by injection or 15 mg/week orally. 12 patients (86%) were on MTX treatment for at least 3 months. The average prednisone dose at 3 months was 11.5 mg/day.

Patient	Months Previously on Corticosteroid	Prednisone dose before MTX (mg)	Time it took to taper completely (months)	Average MTX dose (mg/ week)
1	1.5	60	3	15 PO
2	1	35	3	20 PO
3	0*	20	3	20 SC
4	1.5	80	6	20 SC
5	0*	40	3	20 SC
6	0*	20	6	20 SC
7	5	50	12	20 SC
8	5.5	40	12	20 SC
9	3	15	6	20 SC

*Started corticosteroids the same time they started MTX, but had already been on several prior long courses.
*PO=Oral; SC=Subcutaneous

Table 1: Details on prednisone dosage for patients benefiting from methotrexate.

Of the initial cohort of 14, 3 of ten affected (30%) had improvement of their exophthalmos and 9 (64%) had improvement on their visual acuity, at least one line in the Snellen chart at the 3 month check. Nine patients (64%) were on MTX for at least 6 months. The average corticosteroid dose at 6 months was 2.5 mg/day. Of these 9 patients: 2 (22%) continued to have improvement in their exophthalmos, 3 (33%) continued to show improvement on their visual acuity. Three patients of the initial 14 (21%) continued MTX treatment for at least 12 months. Some patients discontinued methotrexate between 6 and 12 months after starting it because the disease had stabilized and benefit had been optimized based on patient perception. All 3 patients remaining on methotrexate for at least 12 months had tapered their corticosteroid dosage to 0 mg/day. Of these 3 patients, 1 (33%) had improvement of exophthalmos, 3 (100%) had improvement on their visual acuity of at least two lines in the Snellen chart.

Adverse effect	Number of patients
Fatigue	4 (29%)
Nausea	3 (21%)
Hair loss	2 (14%)
Increased Liver Enzymes	2 (14%)
Abdominal Pain	1 (7%)
Headaches	1 (7%)
Dry Skin	1 (7%)

Table 2: Adverse effects of MTX.

Some of the patients experienced a few of the common side effects of MTX. Table 2 lists these adverse effects. Table 3 summarizes the perceived beneficial effects from methotrexate in the trial.

	Number of patients
Patients on prednisone at start of trial	14
Patients able to reduce prednisone dosage to zero	9 out of 14 (64%)
Patients with reduced visual acuity at start of trial	12 (86%)
Patients able to improve acuity by at least two lines	7 out of 12 (58%)
Patients with abnormal exophthalmometry	10 (71%)
Patients with improved exophthalmometry at the end of trial	3 out of 10 (30%)
Patients with EOMs restriction	13 (93%)
Patients with improved EOMs at the end of trial	5 out of 13 (38%)

Table 3: Benefits of methotrexate therapy for TED.

Conclusion

Thyroid eye disease is a presumed autoimmune disease marked by swelling of the muscles and fatty tissues surrounding the eye within the orbit. The first line of treatment in TED is the use of corticosteroid, like prednisone. Corticosteroids are used to treat TED because they appear to be the most effective immunosuppressive agent for soft tissue inflammation, optic neuropathy and extra ocular impairment [11,12]. Corticosteroid treatment has numerous side effects if it is used for a prolonged period of time. Side effects that can be caused by chronic use of corticosteroids include cataracts, fatigue, mood changes, weight gain, sleep loss, easy bruising, redistribution of fat, hair thinning, and diabetes mellitus. Because of these side effects our clinic routinely prescribes methotrexate as a steroid sparing drug. We have previously reported favorable results using methotrexate for a variety of orbital inflammations including 3 patients with Graves' ophthalmopathy [8]. Strianese and colleagues recently reported their results in treating 36 patients with TED with methotrexate without corticosteroid [10]. They used a lower dosage of methotrexate (7.5 to 10 mg/week) compared to our approach. Their study employed a clinical activity score and observed an improvement in extra-ocular motility and no statistically significant change in visual acuity [10]. Methotrexate is an immune suppressive drug that inhibits dihydrofolate reductase enzyme, an enzyme that participates in tetrahydrofolate synthesis, thus inhibiting DNA, RNA and protein synthesis [13]. The rationale to use MTX in TED is because of its immune suppressive properties. One of the effects of inhibiting dihydrofolate reductase is an enhanced extracellular release of adenosine. Adenosine acts on a number of leucocyte subtypes through at least four receptors, having multiple anti-inflammatory effects [8]. Methotrexate also has metabolic effects [14] which potentially contribute to its efficacy in TED. In this trial [14] patients were treated with MTX, either orally or subcutaneously, and corticosteroids. The efficacy of the treatment was measured studying the improvement the patients had in exophthalmos, EOM, VA and how well they could taper off the corticosteroids. The initial average corticosteroid dose was 32 mg. Nine patients succeeded in stopping prednisone completely. There was no marked improvement in exophthalmos at 1, 3, 6 and 12 months. The VA improved at least 2 lines in the Snellen chart in 7 out of 12 (58%) patients who had decreased VA. We did not attempt to estimate how much of the acuity improvement resulted from benefit to the ocular surface and how much resulted from improved function of the optic nerve. EOMs improved slightly in 5 out of 13 patients (38%) who had some restriction. The patients in this trial did not experience serious adverse effects and responded to dose changes of MTX. However, side effects such as gastrointestinal irritation, liver toxicity and bone marrow depression should always be considered. A daily supplement of folic acid was given to all the patients in this trial to minimize the side effects of MTX.

We recognize a variety of limitations to this report. Our observations are retrospective and uncontrolled. It is worth noting that many studies noted favorable effects from rituximab in treating thyroid eye disease [9], but a randomized controlled study failed to show benefit [15]. We did not measure a composite disease activity score. Instead, our primary endpoint was on reduced corticosteroid dosage as an indicator of success. We realize that the natural history of Graves' ophthalmopathy favors gradual improvement. Despite these limitations, our impression is that a subset of patients with thyroid eye disease does derive substantial benefit from methotrexate therapy.

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