Role of methotrexate in thyroid-related orbitopathy

Avi Rubinov, MD,[*] Hila Zommer, MD,[†] Helya Aghazadeh, MD,[†] Ezekiel Weis, MD, MPH[*,†]

ABSTRACT ●

Objective: To report the experience of a tertiary care orbital service in treating severe active thyroid related orbitopathy with methotrexate (MTX) managed by the Ophthalmologist.

Design: Retrospective consecutive case series.

Participants: Nineteen consecutive patients (5 males and 14 females) with severe active thyroid related orbitopathy.

Methods: Severe active thyroid orbitopathy patients with partial or no response to intravenous glucocorticoids were treated with MTX and observed for inflammatory scale reduction and treatment complications.

Results: Nineteen consecutive patients (5 males and 14 females) with severe active thyroid related orbitopathy were evaluated. Mean follow-up time was 1206 days (standard deviation (SD) 576). Months passed from beginning of TRO symptoms to initiation of MTX therapy showed a mean of 12 (SD 9). After the initiation of MTX 91% of eyes demonstrated a clinically significant improvement to a VISA inflammatory scale of <3 within a mean of 189 days (SD 119); A subset of patients (29%) demonstrated a rapid response, reaching a VISA inflammatory score of <3 within 90 days. One patient (5%) discontinued the medication secondary to an adverse event (elevated liver enzymes) which normalized after discontinuation of MTX. During the follow up period 12 patients (63%) have ended their MTX treatment due to TRO inactivity; One patient (8%) developed a recurrence of inflammation after discontinuing MTX which resolved with the re-initiation of MTX treatment. Adjunctive treatments including radiation and/or external beam radiotherapy were administered to 21% of patients.

Conclusion: Our experience suggests that methotrexate managed by an Ophthalmologist is a safe and effective treatment for severe active thyroid related orbitopathy

Thyroid-related orbitopathy (TRO) is a multifactorial autoimmune disease affecting the ocular tissues in 40% of patients with autoimmune hyperthyroidism.[1] TRO has an incidence of 16 female and 3 male cases per 100 000 person-years,[2] with an approximate prevalence of 0.25% and no significant ethnic predilection.[3] The autoimmune orbital disease is believed to be initiated by the activation of inflammatory cells in the orbit, activating a cascade that results in the deposition of glycosaminoglycans and the development of secondary edema.[4] Enlargement of the extraocular muscles in this phase, particularly the medial rectus, can put the patient at risk of developing dysthyroid optic neuropathy.[5,6] Subsequently, the disease progresses into an inactive/noninflammatory phase characterized by fibrosis and adipogenesis.[7–9] Patients with TRO may experience edema, eyelid retraction, ocular surface irritation, diplopia, cosmetic disfigurement, and irreversible visual loss due to permanent corneal changes and dysthyroid optic neuropathy.

Current treatments for the inflammatory/active phase of TRO include immunosuppressive therapy with glucocorticoids, steroid-sparing agents, and radiation therapy. Glucocorticoids currently are the first-line treatment in most centres. In a meta-analysis of 25 articles performed by Bartalena et al. "favorable effects" with the use of glucocorticoids were noted in a majority of, but not all, patients (63%–77%).[10,11] In addition to an incomplete response rate, many concerns remain about the use of glucocorticoids due to potential serious adverse events and the need for long term dosing due to prolonged disease activity and significant recurrence rates after discontinuation.[11,12] Both intravenous and oral glucocorticoid treatments carry a significant risk for the development of adverse events over time. Kahaly et al. have reported adverse events in 51% of patients receiving oral glucosteroids and in 17% receiving intravenous glucocorticoids after 12 weeks of treatment.[13] Recurrence of TRO is common after withdrawal of glucocorticoid treatment, and often several cycles of therapy are needed to achieve adequate control over the disease process. In recent years, the search for newer drugs with better safety profiles and long-term treatment tolerability has shown promising results with several agents.[14–16]

Methotrexate (MTX) is an antimetabolite that inhibits folic acid synthesis, which is required for DNA manufacturing and cell growth. MTX effects include reduction in cell proliferation, T-cell apoptosis, altering cytokine production, and humoral responses.[17] In high doses, MTX is used as a chemotherapeutic agent for different forms of cancer; in lower doses, it is used for long-term treatment of several autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease, and Wegener's granulomatosis.[15]

Published data on the use of MTX for treating orbital inflammation in the setting of TRO are limited to 2 case series, which described a total of 39 cases of TRO.[15,16] The purpose of this study is to report our experience with

http://dx.doi.org/10.1016/j.jcjo.2017.07.009
ISSN 0008-4182/17

Canadian Ophthalmological Society | Société canadienne d'ophtalmologie
EYE PHYSICIANS AND SURGEONS OF CANADA | MÉDECINS ET CHIRURGIENS OPHTALMOLOGISTES DU CANADA

treating severe active TRO with MTX prescribed and managed by an ophthalmologist.

Materials and Methods

This is a retrospective consecutive case series of 19 patients (5 males and 14 females) with severe active TRO treated between 2009 and 2016. The study was approved by the Health Research Ethics Board of Alberta.

Disease activity/inflammation and progression were assessed using the VISA inflammatory score.[18] The inflammatory score calculation was performed by a single ophthalmologist (E.W.) during the physical examination.

This report includes a consecutive case series of all patients with TRO treated with MTX in our orbital service between 2009 and 2016. All patients with severe active orbitopathy were first treated with at least one cycle of intravenous solumedrol (1 g every 48 hours for 3 doses). In cases of minimal, temporary, or no response to intravenous solumedrol, MTX treatment was offered in 3 settings:

1. Very active cases of active TRO, with at least one eye scoring ≥5 on the VISA inflammatory scale
2. Cases of active TRO with at least one eye ≥3 on the VISA (VISA classification system) inflammatory scale and dysthyroid optic neuropathy
3. Cases of active TRO with at least one eye ≥3 on the VISA inflammatory scale with at least 2 out of 4 risk factors for worsening TRO, including older age, male sex, smoking, or a rapid onset of orbitopathy[19]

Because of the expected delay in the onset of action of MTX, all of our patients received another cycle of intravenous steroids at the time of initiating MTX, unless they were currently taking oral steroids prescribed by the referring physician. If they were on long-term oral steroids, these were tapered over approximately 6 weeks. Participants with contraindications to MTX, those under 18 years of age, women interested in conceiving, and those who received MTX for non-TRO orbital inflammatory diseases were excluded.

The main outcome parameter of this study was the decrease in the VISA inflammatory score to <3 during MTX treatment. This was selected as the main outcome because congestion is a significant issue in patients with severe TRO in the noninflammatory phase, making the assessment of changes in the inflammatory scale in the range of 1–2 less valid. Tolerance of MTX, adverse events related to its use, and other modalities used to control inflammation during treatment were also recorded.

Pretreatment laboratory investigations included a complete blood count; liver function tests (including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and bilirubin); kidney function tests (including creatinine and urea); serum electrolytes comprising potassium; and erythrocyte sedimentation rate, hepatitis B and C serology, and hepatitis B immune status. Pretreatment imaging included a chest x-ray.

After screening, patients were started on MTX using a fixed protocol. Patients received 10 mg oral tablets once a week for 4 weeks, followed by 15 mg once a week. Five milligrams of folic acid was given daily, except for the day of MTX administration. Adjustments in dosing were made based on changes in the inflammatory VISA score and side effects 3 months after starting the treatment. Patients were given a standing order for monthly follow-up laboratory examinations, which comprised a complete blood count, liver function tests, kidney function tests, serum electrolytes, and erythrocyte sedimentation rate.

Results

This study included 19 patients with TRO (Table 1) with a mean age of 61.6 years (SD 11.1), and a 73%

Table 1—Patient data showing different parameters surveyed during the study

Patient No.	OD/ OS	Age, years	VISA Score Pretreatment	Maximal Dose of MTX, mg	Days from Start until VISA <3	Comments
1	OD	73	5	15	224	❻
	OS		5		224	❻
2	OD	47	6	10	423	❷
	OS		6		423	❷
3	OD	85	0	20	—	
	OS		6		231	
4	OD	67	7	22.5	434	
	OS		4		105	
5	OD	62	5	17.5	—	❸
	OS		4		67	❶
6	OD	66	6	17.5	105	
	OS		6		105	
7	OD	60	4	20	78	❶❷❺
	OS		4		78	❶❷❺
8	OD	71	5	22.5	266	❹
	OS		5		266	❹
9	OD	50	3	22.5	364	
	OS		3		364	
10	OD	71	3	17.5	182	
	OS		3		182	
11	OD	54	1	20	—	❹
	OS		5		189	❹
12	OD	66	4	15	42	❶
	OS		6		42	❶
13	OD	72	3	15	70	❶
	OS		3		70	❶
14	OD	47	4	15	88	❶
	OS		4		88	❶
15	OD	66	0	20	—	
	OS		5		144	
16	OD	51	6	20	—	❸
	OS		6		—	❸
17	OD	43	0	17.5	—	
	OS		3		68	❶
18	OD	68	4	17.5	230	
	OS		4		230	
19	OD	53	3	15	242	❺
	OS		3		242	❺

❶ VISA score went down to zero after less than 90 days.
❷ IV steroids while on methotrexate (MTX).
❸ Decompression while on MTX because of dysthyroid optic neuropathy.
❹ External beam radiotherapy during MTX treatment.
❺ Elevated liver function tests.
❻ Reactivation after MTX withdrawal.