Methotrexate in the Management of Immune Mediated Cochleovestibular Disorders: Clinical Experience with 53 Patients

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ABSTRACT. ***Objective.*** To describe our experience with low dose weekly methotrexate (MTX) in the management of immune mediated cochleovestibular disorder (IMCVD).

Methods. Between 1991 and 1999, we treated 53 patients with IMCVD with MTX. Patients were selected on the basis of progressive vestibular symptoms that had responded to corticosteroids and in most cases, relapsed. MTX was initiated at a dose of 7.5 mg weekly and increased to doses up to 25 mg weekly as needed. Response was assessed by audiologic studies and history of change in tinnitus and vertigo. MTX was discontinued after 4–6 mo in patients showing no improvement, and after 12–18 mo in patients with improved and stable symptoms.

Results. Three patients were still in early therapy and had not improved. Of the 50 remaining patients, significant improvement was seen in vertigo in 27/39 (69%) patients, hearing loss in 25/47 (53%), and tinnitus in 11/42 (26%). Overall improvement in symptoms was seen in 35/50 (70%) patients. Four patients stopped MTX due to toxicity, and 11 due to lack of response. In 28 patients, MTX was stopped after 12–18 mo when symptoms had stabilized, and restarted in 5 of these after relapse. Seven patients remain on therapy with improved and stable symptoms after 17.3 mo.

Conclusion. In this open label experience, a majority of patients with IMCVD improved with weekly low dose MTX therapy with minimal toxicity. (J Rheumatol 2001;28:1037–40)

Key Indexing Terms:
METHOTREXATE HEARING LOSS MENIERE'S DISEASE

McCabe first suggested an autoimmune basis for hearing loss and vertigo in some patients in 1979, when he reported on a series of patients with idiopathic sensorineural hearing loss responsive to corticosteroid and immunosuppressive therapy[1]. Since this original description, this entity has been given a variety of names, including autoimmune hearing loss and immune mediated cochleovestibular disorder (IMCVD). A number of clinical, histologic, and serologic observations as well as animal models have attempted to further define this disorder[2-7]. Patients typically present with bilateral progressive sensorineural hearing loss with or without vertigo, tinnitus, and aural fullness. Antibodies to inner ear antigens can be detected in the serum of some patients and have been associated with steroid responsiveness. The diagnosis of IMCVD is made by excluding other causes of vestibular dysfunction and demonstrating improvement of symptoms with corticosteroid or other immunosuppressive therapy. Traditional therapy has consisted of high dose corticosteroids and cyclophosphamide in selected patients. However, due to the variable natural history of the disorder, treatment is usually individualized according to drug tolerance and treatment response[4,8,9]. As an alternative to these therapies, we reported on the use of weekly oral methotrexate (MTX) in the management of this condition, with a favorable response noted in a majority of patients[10-12].

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MATERIALS AND METHODS

All patients with a diagnosis of IMCVD treated with weekly oral MTX at our institution between 1991 and 1999 were followed prospectively. Most patients were treated initially with corticosteroids to improve symptoms, and MTX was added to stabilize or further improve symptoms. The diagnosis of IMCVD was based on the following criteria: (1) presence of progressive sensorineural hearing loss or cochleovestibular symptoms such as episodic vertigo, tinnitus, and/or aural fullness; and (2) a positive response to prednisone (1 mg/kg/day) given over 2–4 weeks or to intratympanic steroids. The response to prednisone was considered to be positive if there was either (1) audiologic improvement of pure tone average (500, 1000, 2000 Hz) greater than 10 dB and/or 12% increase in word discrimination; and/or (2) elimination of or significant improvement in vertigo and disequilibrium by patient report.

All patients were evaluated and followed by a rheumatologist with

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complete history, examination, and laboratory studies as appropriate to exclude systemic inflammatory or autoimmune disorders that might be associated with unexplained hearing loss or vertigo. Patients with a history of regular alcohol use or underlying liver or renal disease were not treated with MTX. A Western blot test for the detection of antibodies against inner ear antigens was performed for 24 patients[3]. Appropriate imaging studies were performed to rule out retrocochlear lesions for all patients.

Patients were given MTX in most cases after a trial of steroids had showed improvement. Steroids were tapered and discontinued in most patients over 3–6 weeks. MTX was initiated at a dose of 7.5–12.5 mg/week and the dosage was increased to 12.5–25 mg/week as tolerated to achieve maximum response. Folic acid (1–3 mg) was given daily to minimize complications such as stomatitis, nausea, and malaise. In some patients, prednisone was restarted for brief periods of time for exacerbations, and tapered as tolerated. Some patients continued taking chronic low doses of prednisone while taking MTX. Blood chemistry evaluation of renal and liver function and complete blood count with differential were checked every 6 to 12 weeks while on therapy.

Pure tone average and speech audiometry were obtained at monthly intervals for the first 6 months and every 2–3 mo thereafter. The pretreatment audiogram was compared with the most recent audiogram. Improvement in hearing was defined as an increase of more than 10 dB on pure tone average and/or 12% improvement in word discrimination score. Changes in vertigo and tinnitus were based upon patient survey as either improved or persistent. A patient was considered to have a positive overall response if there was subjective and objective improvement in the predominant symptom (hearing loss or vertigo), without worsening of other symptoms or findings. MTX was usually discontinued after 4–6 mo in patients without significant response. In most patients that showed improvement and stabilization of symptoms, MTX was tapered and discontinued after 12–18 mo of therapy, and reinstituted later as needed for exacerbations.

RESULTS

Fifty-three patients were treated with MTX during the period of observation. The demographic characteristics and presenting symptoms of these patients are summarized in Table 1. Diseases or laboratory abnormalities with a possible relationship to vestibular dysfunction were identified in 9 patients, although vestibular dysfunction was not felt to be a manifestation of these conditions in any case. A wide range of symptom duration was seen in this group, with most having over a year of symptoms prior to treatment. Most patients had a combination of hearing loss, tinnitus, and vertigo. Vertigo and hearing loss were the predominant symptoms in similar numbers of patients. Four patients had previously undergone surgical procedures (neurectomy or endolymphatic shunt) for their conditions, with incomplete response. Seven patients had not received corticosteroids prior to MTX therapy due to contraindications (diabetes, hypertension, and previous intolerance). Four patients had been treated with intratympanic corticosteroid injection with good response. Oral corticosteroids had been given to 42 patients, with a poor response in 2 patients and intolerance in 2 patients. Thirty-eight patients had good responses to corticosteroids; 16 of these had relapsed after an initial course, 13 had experienced multiple relapses after steroid trials, and 9 started taking MTX as their initial course of steroids were tapered. Antibodies against inner ear antigens were detected in 11/23 patients tested.

Table 1. Clinical characteristics of 53 patients with immune mediated cochleovestibular disorders treated with methotrexate.

Demographics n (%)		
Male 25 (47)		
Female 28 (53)		
Caucasian 42 (79)		
African-American 11 (21)		
Mean Age (range) (years) 50.5 (7–78)		
Potential associated disease or baseline laboratory studies n (%)		
None	44 (83)	
Possible	9 (17)	
systemic lupus erythematosus (2)		
possible Cogan's syndrome (2)		
ankylosing spondylitis (1)		
possible systemic vasculitis (1)		
monoclonal gammopathy (1)		
post-immunization (1)		
high-titer ANA (1)		
Mean duration of symptoms (range, mos 52.4 (range 1–192)		
Distribution (n)	≤ 1 year	(17)
	1–5 years	(17)
	≥ 5 years	(19)
Symptoms (n)		
Hearing loss	50 (predominant symptom in 27)	
Vertigo	41 (predominant symptom in 26)	
Tinnitus	43	

The mean weekly dose of MTX was 14.3 mg (range 7.5–25 mg). MTX was well tolerated in the group as a whole with a minority of patients experiencing mild nausea, malaise, and/or stomatitis. No hematologic or hepatic toxicity was seen in any patient. Therapy was discontinued due to toxicity in 4 patients, all within the first 4 mo of therapy [nausea, stomatitis (2), and possible pneumonitis].

Three patients had not responded after 2–4 mo and were still being followed on therapy. Response was analyzed in the remaining 50 patients taking MTX after corticosteroids were tapered (Table 2). Significant improvement or resolution of tinnitus was seen in 11/42 (26%) patients. Hearing loss improved significantly in 25/47 (53%) patients. Vertigo resolved or significantly improved in 27/39 (69%) patients. Worsening of tinnitus, hearing loss, or vertigo was not seen in any patient. Overall, 35/50 patients were considered responders (70%) and 15 (30%) nonresponders. Twelve patients were treated with repeated short courses or continuous low doses of prednisone (5–15 mg daily) while being treated with MTX, including 8 of the 35 responders and 4 of the 15 nonresponders.

Table 2. Response to methotrexate in 50 patients with IMCVD.

Symptom (n)	Improved (%)	Unchanged (%)	Worse (%)
Vertigo (39)	27 (69)	12 (31)	0 (0)
Hearing loss (47)	25 (53)	22 (47)	0 (0)
Tinnitus (42)	11 (26)	31 (74)	0 (0)
Overall response (50)	35 (70)	15 (30)	0 (0)

(No response after 2–4 months in 3 patients, not included in analysis).

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Table 3. Current status of 53 patients with IMCVD treated with methotrexate.

	n
Nonresponders (18)	
No response on early therapy (2–4 mos)	3
Stopped due to toxicity (mean 1.9 mos)	4
Stopped due to lack of response (mean 8.1 mos)	11
Responders (35)	
Improved and remained on therapy (mean 17.3 mos)	7
Stopped after stable symptoms (after mean 15.8 mos)	28
Restarted after relapse (2–12 mos later)	5
Remain off therapy and stable	23

The current status of all 53 patients is summarized in Table 3. Forty-three patients had stopped therapy after a mean duration of therapy of 12.7 mo. Four of these were stopped due to toxicity (as noted above, at a mean of 1.9 mo) and 11 due to a lack of response after a mean of 8.1 mo. Twenty-eight patients stopped therapy after good control and stabilization of symptoms after a mean of 15.8 mo. In 5 of these patients, symptoms relapsed within 2–12 mo after discontinuation, and MTX was reinstituted (with prednisone in one patient) with subsequent improvement. Two patients eventually required labyrinthectomy or vestibular nerve resection for recurrent exacerbations or persistent stable symptoms. Seven patients continue taking MTX with improvement and stabilization of symptoms, and have been on therapy for a mean of 17.3 mo. Three patients in the early phase of treatment are unimproved and remain on therapy after 2–4 mo. One patient has been treated with the addition of other immunosuppressive agents to MTX after an incomplete response of disabling vertigo to MTX alone. This patient responded poorly to MTX with azathioprine, and is now improved and stable taking a combination of MTX and cyclosporine.

No difference in overall response was seen in patients stratified by duration of symptoms, with improvement seen in 11/16 with ≤ 1 year of symptoms, 9/15 with 1–5 years of symptoms, and 15/19 with ≥ 5 years of symptoms. The 7 patients treated with MTX alone had a similar frequency of responders (4/7, 57%) compared to those treated initially with steroids. The 9 patients identified with possible underlying conditions showed a response rate similar to the entire group (5/9, 56%). No difference in overall response was seen in patients with positive autoantibody tests (8/11) compared to those with negative autoantibody tests (9/13).

DISCUSSION

McCabe first described autoimmune hearing loss in 1979, reporting a series of 18 patients with a combination of hearing loss and vestibular dysfunction that responded to therapy with high dose corticosteroids and intravenous cyclophosphamide[1]. Since that time, reports have described the response of this syndrome to regimens of immunosuppressive agents. Hughes, *et al* reported on 47 patients treated with prednisone, initially at 1 mg/kg/day for 10–20 days, followed by 10 mg every other day for up to several months[8]. In this series, hearing loss improved in 40% of patients, stabilized in 45%, and worsened in 15%. Vertigo improved in 71% and tinnitus in 82% of patients. Harris and Darmstadt recommended 30 mg of prednisone twice daily for 2 weeks followed by alternate day therapy with the lowest dose possible[13]. Treatment continued for at least 6 to 12 months and occasionally up to 2 years, and cyclophosphamide was added for patients who failed to respond to steroid therapy. McCabe later reported greater than 95% favorable results using a regimen of prednisone and oral cyclophosphamide in a series of 66 patients[4]. In this report, patients were treated initially with prednisone 30 mg daily and cyclophosphamide 2 mg/kg/day for 3 mo, with reinstatement for an additional 3 mo for patients with recurrent symptoms. Some patients required treatment for up to 24 mo, with alopecia being the most commonly encountered toxicity. In a smaller series, Cotter reported improvement in hearing in 9 of 12 patients and vertigo in 3 of 6 patients treated with a regimen of oral steroids followed by cyclophosphamide[9]. In another small series, plasmapheresis followed by 3 mo of immunosuppressive therapy has also been reported to be helpful in improving auditory function in 6 of 8 patients[14].

Based on the above reports, cyclophosphamide appears to be an effective therapy for IMCVD, and a potential alternative to longterm corticosteroid treatment for patients with persistent disabling symptoms. Unfortunately, extended followup of patients treated with cyclophosphamide for other benign conditions has been associated with a high incidence of serious drug related toxicities, including infertility, myeloproliferative disorders, and transitional cell carcinoma of the bladder[15]. MTX has a much more favorable longterm safety profile than cyclophophamide, and is often considered as an alternative for conditions that require longterm immunosuppressive therapy[16]. Since the mid 1980s, MTX has been used widely in patients with rheumatoid arthritis with a favorable efficacy and toxicity profile, and has become the most frequently used disease modifying agent in this condition[17]. In addition, MTX has also been used as immunosuppressive therapy in a wide variety of other nonneoplastic conditions, including systemic lupus erythematosus, polymyositis, Cogan's syndrome, and Wegener's granulomatosis[18,19].

We began using MTX for IMCVD in 1991, and have noted improvement in vertigo, hearing loss, and tinnitus in a majority of patients in these earlier reports. As in previous reports, we have continued to see substantial overall improvement in about 70% of patients. In particular, we have seen substantial improvement or complete resolution in over half of our patients with hearing loss, in over two-thirds of patients with vertigo, and in about one-quarter of

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patients with tinnitus. Some patients have had complete resolution of symptoms, while many continue to have some degree of unsteadiness, hearing deficit, or low grade tinnitus. Patients have tolerated MTX, with few patients stopping due to toxicities. The degree of response in this series of patients has been comparable to that described in previous reports using corticosteroids and cyclophosphamide.

The natural history of IMCVD is still poorly understood. Many patients seem to have a relatively brief, self-limited process which responds completely to corticosteroid therapy without recurrence, while others have symptoms for many years and represent a subset of patients with chronic Meniere's disease[6]. Our report describes the open label use of MTX in patients with IMCVD who have responded to steroid therapy, but does not constitute a placebo-controlled trial. Most of the patients had a long history of idiopathic cochleovestibular dysfunction or had experienced a relapse of symptoms after an initial trial of corticosteroids. Thus, it is unlikely that either spontaneous improvement or placebo effect is responsible for the level of improvement seen in this cohort of patients. Most patients who responded to therapy continued taking MTX for over a year once symptoms were stabilized, and therapy was stopped. The variable duration of symptoms prior to therapy and the relapse of symptoms in 5 of the 28 patients after discontinuation further emphasize the heterogeneity of this condition as it is currently characterized. The recent observation of autoantibodies to inner ear antigens as a predictor of response suggests a means by which patients can be selected to receive steroid and immunosuppressive therapy[3]. However, we did not see a correlation between the presence of these autoantibodies and steroid response in those patients who were tested.

We were able to observe sustained improvement with the use of weekly MTX in a majority of our patients with IMCVD, most of whom had relapsed after prior corticosteroid therapy was discontinued. This therapy was well tolerated, and most patients have been able to stop therapy after 1–2 years without recurrence of symptoms. In a clinical syndrome in which diagnostic standards are still uncertain and natural history is poorly understood, MTX should be considered for patients with disabling hearing loss and/or vertigo as an alternative to chronic corticosteroid therapy or cyclophosphamide. Further definition of the pathogenesis and natural history of this condition and placebo controlled studies are need to better define the optimal approach to diagnosis and treatment of patients with idiopathic cochleovestibular disorders.

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