• Clinical Research •

Methotrexate for chronic non-necrotizing anterior scleritis in Chinese patients

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Abstract

● **AIM:** To evaluate the effectiveness and corticosteroid-sparing capabilities of methotrexate (MTX) in the treatment of chronic non-necrotizing anterior scleritis in Chinese patients.

● **METHODS:** A retrospective chart review of all patients with active anterior scleritis between January 2015 and June 2019 was conducted. All patients received 10 to 15 mg/wk MTX orally, and corticosteroids (10 to 40 mg/d prednisolone or equivalent methylprednisolone) with slow tapering. Topical corticosteroid eye drops (1% prednisolone actate, 0.1% dexmathosone or 0.1% fluoromethalone) were applied to control comorbid anterior uveitis at presentation or during follow up. The main outcomes were inflammation control and corticosteroid-sparing success, and secondary outcomes were reduction of immunosuppression load and best-corrected visual acuity (BCVA).

● **RESULTS:** Thirty-two eyes (22 patients) were included. The proportion of patients who achieved corticosteroid-sparing success was 50.0% at 3mo and 77.3% at 12mo [8 (36.4%) patients discontinued corticosteroid]. The proportion of eyes that achieved inflammation control was 59.4% at 3mo and 78.1% at 12mo. The immunosuppression load was 5.14±0.87 at presentation and 2.76±2.34 at 12mo (P<0.01). BCVA maintained unchanged or improved in 29 (90.6%) of all affected eyes. One patient discontinued MTX treatment because of an abnormal liver function test, and no other serious adverse effects were observed.

● **CONCLUSION:** According to this pilot study, low dose MTX appear to be a well-tolerated and effective treatment for chronic non-necrotizing anterior scleritis patients in the Chinese population.

● **KEYWORDS:** methotrexate; non-necrotizing anterior scleritis; pharmacotherapy; corticosteroid-sparing; Chinese population

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INTRODUCTION

Anterior scleritis, mostly mediated by autoimmune mechanisms, is an ocular inflammatory disease presented as redness and pain of the sclera. Persistent or recurrent non-infectious anterior scleritis may lead to visual threatening ocular complications including scleral thinning, keratitis, uveitis, glaucoma, and cataract[1]. An underlying systemic disease is frequently present in patients with anterior scleritis[2]. Reported comorbidities included rheumatoid arthritis (RA), ankylosing spondylitis (AS), relapsing polychondritis (RP), inflammatory bowel disease (IBD), granulomatosis with polyangiitis (GPA), and systemic lupus erythematosus (SLE)[3-9]. Anterior scleritis can be categorized into necrotizing, nodular, and diffuse subtypes. The necrotizing subtype is the most severe and destructive subtype which warrants aggressive immunosuppressive treatment, the non-necrotizing forms are usually less progressive.

Treatment of acute anterior scleritis depends on the severity of the disease. While oral nonsteroidal anti-inflammatory drug (NSAID) is adequate for some mild patients, oral corticosteroid remains the mainstay treatment for more severe cases. Immunomodulatory treatment (IMT) is often considered to spare corticosteroid when long-term immunosuppression is required[10]. Methotrexate (MTX) is a folic acid analog

and competitive inhibitor of dihydrofolate reductase. By blocking the conversion of dihydrofolate to tetrahydrofolate and inhibiting cell division, MTX has both antiproliferative and anti-inflammatory effects[11-12]. While MTX has been well known as the first-line corticosteroid-sparing agent for pediatric uveitis[13-15]. The promising effect of MTX on non-necrotizing anterior scleritis is suggested by studies from western countries[15-18]. However, only a few studies have demonstrated the use of immunosuppressive treatments for scleritis or other ocular inflammatory diseases in Asian populations[6,19]. To the best of our knowledge, this study is one of the first studies that reported the safety and efficacy of low-dose MTX in Chinese patients with non-necrotizing anterior scleritis.

SUBJECTS AND METHODS

Ethical Approval This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Peking Union Medical College Hospital (PUMCH; S-K1363-2). This was a single-center retrospective comparative study. Written and verbal consent for participation in the study was obtained from all participants.

Patients Patients who were diagnosed with non-necrotizing anterior scleritis and had received oral MTX to control active scleritis between January 2015 and June 2019 at the Department of Ophthalmology, PUMCH were retrospectively reviewed. The patients met any of the following criteria were excluded in this study: 1) allergy and intolerance to MTX; 2) duration of MTX was less than 3mo; 3) duration of follow-up after initiation of MTX was less than 1y; 4) the patient had been on MTX before the development of scleritis for comorbid systemic disease; 5) the patients had been on biologics (such as anti-tumor necrosis factor agents), or has increased the dose of other IMT agents (cyclosporin A, azathioprine, tacrolimus, mycophenolate, *etc*.), or had undergone periocular corticosteroid injection or ocular surgery, within 6mo before initiation of MTX or during follow up; 6) had positive findings for any infectious etiology.

Treatment Before institution of IMT, history of recurrent or chronic infections was excluded, and blood cell count, liver functions, renal functions, hepatitis B virus, hepatitis C virus, blood T-SPOT. Tuberculosis (TB) antinuclear antibodies and chest X-rays were screened for baseline assessment and to exclude potential contraindications. MTX was considered for patients who required ≥3mo of systemic corticosteroids (≥10 mg/d) for inflammation control or when corticosteroids were not tolerated. In all patients, oral corticosteroid was given before or concomitantly with MTX, and the initial dose was prednisolone 10-40 mg/d or equivalent methylprednisolone. Corticosteroid was slowly tapered depending on disease severity and the patients' responsiveness to treatment and stopped when scleritis had been quiescent for at least 3mo with minimal dose (≤5 mg/d prednisone or equivalent) of corticosteroid. Topical corticosteroid eye drops (1% prednisolone actate, 0.1% dexmathosone or 0.1% fluoromethalone) with proper tapering schedule were applied to control comorbid anterior uveitis in accordance with international consensus at presentation or during follow up[20]. Blood tests, including blood cell count, liver and kidney functions were obtained every 1 to 3mo to monitor potential side effects of MTX. The initial oral dose of MTX was 10-15 mg/wk, with 5 mg folic acid supplemented the next day after the MTX dose to lower the risk of gastrointestinal side effects. Follow-up visits were scheduled every 1-2wk at the active phase and every 1-3mo at the quiescent phase. A complete ophthalmic examination including best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp examination of the sclera and anterior segment, and fundoscopy was performed at each visit. The data collected included the patients' age, sex, follow-up period, topical and systemic treatments, ocular complications, associated systemic diseases, BCVA in the form of logarithm of the minimum angle of resolution (logMAR) units.

Data Analysis The main outcomes were corticosteroid-sparing success and inflammation control. Corticosteroid-sparing success was defined as oral prednisone ≤10 mg/d for longer than 1mo with stable or continuously improving scleral inflammation. The active phase of scleritis was defined as ≥1+ (mild scleral inflammation with diffuse mild dilation of deep episcleral vessels)[21] in at least one quadrant. Inflammatory control was defined as complete resolution of scleral redness and pain in the affected eye without recurrence. The calculation of immunosuppressive load was based on the scoring system proposed by Nussenblatt *et al*[22], in which different immunosuppressive agents have scores ranging from 0-9 in each dose of the drug. And the amount of tacrolimus was converted to cyclosporine based on the literature to do the calculation[23]. The paired Student's *t*-test was used for statistical analyses.

RESULTS

Baseline Characteristics Thirty-two affected eyes of 22 patients (16 females and 6 males) with a median age of 48.2±15.5y (range 20-80y) were included in this study. The demographic and clinical characteristics of the patients are summarized in Table 1. Sixteen patients were diagnosed with diffuse anterior scleritis and 6 patients with nodular anterior scleritis. The mean duration of active scleritis before starting MTX treatment was 2.3±1.7mo (range: 1 to 8mo). Systemic diseases were identified in 22.7% of the patients, among which 5 (22.7%) patients had an associated systemic disease with 3 patients had RP and 2 had RA, 3 (2 RP, 1 RA) had been on tacrolimus 1 or 2 mg/d without dose up-titration within 6mo before and during follow up after initiation of MTX. In total, 59.1% of the patients were treated with topical corticosteroids.

Effectiveness of Methotrexate All eyes had active scleritis at the time when MTX was initiated. The proportion of eyes that achieved inflammation control was 59.4% (19/32), 65.6% (21/32) and 78.1% (25/32) 3mo, 6mo, and 12mo respectively after the addition of MTX (Figure 1). BCVA was found to be improved, unchanged, and decreased in 20 eyes (62.5%), 9 eyes (28.1%) and 3 eyes (9.4%, 2 due to development of cataract) respectively.

The proportion of patients that achieved corticosteroid-sparing success was 50.0% (11/22), 77.3% (17/22), and 77.3% (17/22) 3mo, 6mo, and 12mo respectively after MTX treatment, with 8 (36.4%) patients completely discontinued oral corticosteroid (Figure 2). After initiation of MTX, the average dose of systemic corticosteroid significantly decreased from 22.50 mg/d of prednisone or equivalent to 3.47 mg/d at 12mo observation period (P<0.01). The immunosuppression load was 5.14±0.87 and 2.76±2.34 (P<0.01) before and 12mo after MTX treatment respectively. Treatment failure occurred in 22.7% (n=5) of the patients, of whom 3 had stopped MTX and 2 were on MTX when the eye became re-inflamed. They required additional therapy, and cyclophosphamide (n=2) or tacrolimus (n=3) was administered to these patients.

Safety Analysis Complications were observed in 13 (59.1%) patients. Interstitial keratitis was the most common complication and was observed in 6 patients (27.3%; 4 had keratitis before initiation of MTX); scleral thinning, anterior uveitis, elevated IOP, and development of cataract were observed in 4, 4, 3 and 2 patients during follow up, respectively. Temporary elevation of liver enzymes was observed in 1 patient (4.5%) which result in withdraw of MTX, and no other serious drug-related adverse event was documented.

DISCUSSION

Uncontrolled non-necrotizing anterior scleritis usually causes protracted ocular redness and pain which may seriously affect the patient's daily activities and quality of life. Due to its low prevalence, reports on anterior scleritis in the Chinese population were scarce, and most of the ophthalmologists in this country are unfamiliar with the diagnosis and long-term treatment of anterior scleritis. Oral corticosteroids are commonly used as the first-line treatment, but they may cause significant side effects as a long-term maintenance therapy including glaucoma, cataract, elevated blood pressure and blood sugar, gastric ulcers, psychiatric effects, osteoporosis, *etc* [24]. Disease recurrence during tapering of oral corticosteroids is also frequently encountered. IMT is an important complementary for oral corticosteroid and MTX is recommended to be the IMT agent of choice for anterior scleritis based on the number of reports from the western counties[15-16,25]. However, it is less well studied in the Chinese population, which highlights the value of the current study.

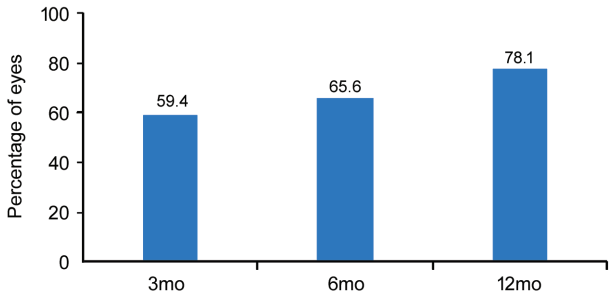

Figure 1 The proportion of eyes that achieved inflammation control during follow-up months.

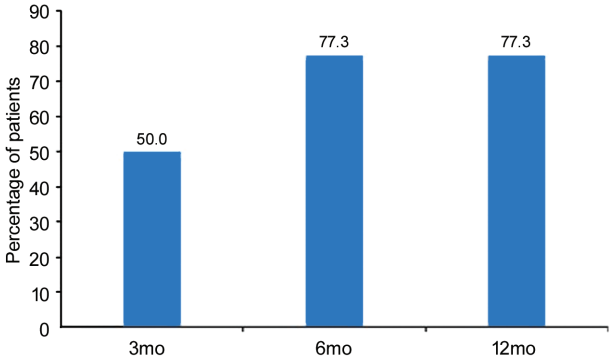

Figure 2 The proportion of patients that achieved corticosteroid-sparing success during follow-up months.

Table 1 Demographic and clinical characteristics of patients with non-necrotizing anterior scleritis

Parameters	*n* (%)
Gender	
Male	6 (27.3)
Female	16 (72.7)
Duration of active scleritis before MTX (mo)	
Mean	2.3±1.7
Range	1-8
Bilaterality	10 (45.5)
Scleritis type	
Diffuse anterior scleritis	16 (72.7)
Nodular anterior scleritis	6 (27.3)
Anterior segment ocular complications	
Anterior chamber cells	4 (18.2)
Peripheral ulcerative keratitis	4 (18.2)
Ocular hypertension	3 (13.6)
Scleral thinning	4 (18.2)
Associated systemic diseases	
Total	5 (22.7)
Relapsing polychondritis (RP)	3 (13.6)
Rheumatoid arthritis (RA)	2 (9.1)
Concomitant medications	
Tacrolimus 1 mg Qd or Bid	3 (13.6)
Topical corticosteroids	13 (59.1)

Qd: Once daily; Bid: Twice a day; MTX: Methotrexate.

Subsequent studies with different evaluation criteria, dosing regimens of MTX and accompanying treatments continued to reveal generally favorable effectiveness of MTX on non-

necrotizing anterior scleritis. In Jachens and Chu's study[17], 64.7% of their scleritis patients achieved inflammation control which was defined as a resolution of inflammation in the affected eyes for 3mo or longer. In Wieringa *et al*'s report[25], however, only 47% (17/36) patients achieved disease quiescence for longer than 3mo with less than 10 mg daily oral prednisone with or without IMT. The maintenance doses of MTX in Jachens and Chu[17] and Wieringa *et al*[25] studies were 20 mg/wk, 30 mg/wk orally, respectively. More promising results were reported by David *et al*[16] with 90.5% and 92.3% of their patients achieved inflammation control and steroid-sparing success respectively at doses between 15 and 25 mg/wk, but 4 patients (5 eyes) also underwent periocular corticosteroid injections during the treatment period. In some studies, favorable responses were observed when a lower-dose of MTX (10 to 15 mg/wk) was adopted[15,26].

In our study, corticosteroid-sparing success was achieved in 77.3% of patients with sustained disease quiescence in 78.1% of the eyes 12mo after initiation of MTX. Of the 5 patients who underwent scleritis relapse, 3 had withdrawn MTX when inflammation recurred, disclosing a lower recurrence rate in patients maintained with MTX. In addition, the maximum dose of MTX was 15 mg/wk during the whole follow-up period and no periocular injections were used or has increased the dose of other IMT agents, suggesting the promising role to achieve treatment success of low dose MTX for Chinese patients with non-necrotizing anterior scleritis. Our study revealed also higher tolerability of long-term MTX than previous studies. Compared to 6%[17] to 11.8%[16] of intolerance observed in previous studies, serious side effects that result in discontinuation of MTX were only observed in 4.5% of patients, which indicates that monitoring the cumulative adverse effects of MTX is still important. Probably due to different pharmacogenetics in the East Asian population, the recommended dose of MTX is usually lower than the western countries[27]. The recommended dose for a particular patient in our study was based on disease severity and tolerance. The lower dosing regimen of MTX adopted might explain at least in part the better safety profile in our study.

Our study also revealed a lower rate (22.7%) of systemic comorbidities than previous studies, which were reported to range between 23.4% and 57.0%[28-29]. In addition, RP was found to be the most common associated systemic condition in our study, which was reported to be, as compared to RA[25,30], a relatively minor cause of scleritis involving 0.96% to 6.39% of patients[31-32]. However, whether our study revealed a distinctive clinical profile of Chinese anterior scleritis patients or just an anecdotal finding requires further validation.

One should also keep in mind the limitations of our current study. Selection biases are inevitable due to the tertiary referral center-based, retrospective nature of the study. The sample size is also limited. Nevertheless, this study is one of the first pilot studies that evaluated low dose MTX for chronic, noninfectious, non-necrotizing anterior scleritis in the Chinese population thus may serve as a good reference.

In conclusion, low dose MTX appeared to be a well-tolerated and generally effective treatment in patients with non-necrotizing anterior scleritis patients in the Chinese population. Multi-center studies with longer follow-up and larger sample sizes are needed in the future to validate our results.

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REFERENCES

1 Dutta Majumder P, Agrawal R, McCluskey P, Biswas J. Current approach for the diagnosis and management of noninfective scleritis. *Asia Pac J Ophthalmol* 2020;Publish Ahead of Print(2).

2 Daniel Diaz J, Sobol EK, Gritz DC. Treatment and management of scleral disorders. *Surv Ophthalmol* 2016;61(6):702-717.

3 Murthy SI, Sabhapandit S, Balamurugan S, Subramaniam P, Sainz-de-la-Maza M, Agarwal M, Parvesio C. Scleritis: differentiating infectious from non-infectious entities. *Indian J Ophthalmol* 2020;68(9):1818-1828.

4 Turk MA, Hayworth JL, Nevskaya T, Pope JE. Ocular manifestations in rheumatoid arthritis, connective tissue disease, and vasculitis: a systematic review and metaanalysis. *J Rheumatol* 2021;48(1):25-34.

5 Yang PZ, Ye Z, Tang JH, Du LP, Zhou QY, Qi J, Liang L, Wu LL, Wang CK, Xu M, Tian Y, Kijlstra A. Clinical features and complications of scleritis in Chinese patients. *Ocular Immunol Inflamm* 2018;26(3):387-396.

6 Hiyama T, Harada Y, Kiuchi Y. Clinical characteristics and efficacy of methotrexate in Japanese patients with noninfectious scleritis. *Jpn J Ophthalmol* 2021;65(1):97-106.

7 Ottaviano G, Salvatore S, Salvatoni A, Martelossi S, Ventura A, Naviglio S. Ocular manifestations of paediatric inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis* 2018;12(7):870-879.

8 Shenavandeh S, Petramfar P. Three atypical manifestations of granulomatosis with polyangiitis: lateral medullary syndrome, anterior cheek mass and melting scleritis of eye. *Reumatologia* 2017;55(3): 145-150.

9 Sumethkul K, Urailert I, Kitumnuaypong T, Angthararak S, Silpa-Archa S. The incidence, risk factor, and time to develop rheumatologic diseases after isolated inflammatory eye diseases: a 12-year cohort study. *Clin Rheumatol* 2022;41(4):1003-1012.

10 Rathinam SR, Gonzales JA, Thundikandy R, *et al*, Group FASTR. Effect of corticosteroid-sparing treatment with mycophenolate mofetil *vs* methotrexate on inflammation in patients with uveitis: a randomized clinical trial. *JAMA* 2019;322(10): 936-945.

11 Bedoui Y, Guillot X, Sélambarom J, Guiraud P, Giry C, Jaffar-Bandjee MC, Ralandison S, Gasque P. Methotrexate an old drug with new tricks. *Int J Mol Sci* 2019;20(20):E5023.

12 Maksimovic V, Pavlovic-Popovic Z, Vukmirovic S, Cvejic J, Mooranian A, Al-Salami H, Mikov M, Golocorbin-Kon S. Molecular mechanism of action and pharmacokinetic properties of methotrexate. *Mol Biol Rep* 2020;47(6):4699-4708.

13 Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. *J Rheumatol* 2005;32(2):362-365.

14 Malik AR, Pavesio C. The use of low dose methotrexate in children with chronic anterior and intermediate uveitis. *Br J Ophthalmol* 2005;89(7):806-808.

15 Kaplan-Messas A, Barkana Y, Avni I, Neumann R. Methotrexate as a first-line corticosteroid-sparing therapy in a cohort of uveitis and scleritis. *Ocul Immunol Inflamm* 2003;11(2):131-139.

16 Sands DS, Chan SCY, Gottlieb CC. Methotrexate for the treatment of noninfectious scleritis. *Can J Ophthalmol* 2018;53(4):349-353.

17 Jachens AW, Chu DS. Retrospective review of methotrexate therapy in the treatment of chronic, noninfectious, nonnecrotizing scleritis. *Am J Ophthalmol* 2008;145(3):487-492.e2.

18 Bernauer W, Pleisch B, Brunner M. Five-year outcome in immune-mediated scleritis. *Graefes Arch Clin Exp Ophthalmol* 2014;252(9): 1477-1481.

19 Jeon HS, Hyon JY, Kim MK, Chung TY, Yoon KC, Kim JY, Na KS, Kim HJ, Kim TI, Lee JS, Lee HK, Song JS. Efficacy and safety of immunosuppressive agents in the treatment of necrotising scleritis: a retrospective, multicentre study in Korea. *Br J Ophthalmol* 2016;100(8):1066-1070.

20 Harthan JS, Opitz DL, Fromstein SR, Morettin CE. Diagnosis and treatment of anterior uveitis: optometric management. *Clin Optom* (*Auckl*) 2016;8:23-35.

21 Sen HN, Sangave AA, Goldstein DA, Suhler EB, Cunningham D, Vitale S, Nussenblatt RB. A standardized grading system for scleritis. *Ophthalmology* 2011;118(4):768-771.

22 Nussenblatt RB, Peterson JS, Foster CS, Rao NA, See RF, Letko E, Buggage RR. Initial evaluation of subcutaneous daclizumab treatments for noninfectious uveitis. *Ophthalmology* 2005;112(5):764-770.

23 Shimada H, Uchida J, Kosoku A, Iwai T, Kabei K, Nishide S, Naganuma T, Kumada N, Takemoto Y, Nakatani T. Conversion from cyclosporine to once-daily tacrolimus on 50:1 Mg basis: a short-term pilot study. *Exp Clin Transplant* 2020;18(1):1-7.

24 Oray M, Abu Samra K, Ebrahimiadib N, Meese H, Foster CS. Long-term side effects of glucocorticoids. *Expert Opin Drug Saf* 2016;15(4):457-465.

25 Wieringa WG, Wieringa JE, ten Dam-van Loon NH, Los LI. Visual outcome, treatment results, and prognostic factors in patients with scleritis. *Ophthalmology* 2013;120(2):379-386.

26 Pincus T, Furer V, Sokka T. Underestimation of the efficacy, effectiveness, tolerability, and safety of weekly low-dose methotrexate in information presented to physicians and patients. *Clin Exp Rheumatol* 2010;28(5 Suppl 61):S68-S79.

27 Kameda H, Fujii T, Nakajima A, Koike R, Sagawa A, Kanbe K, Tomita T, Harigai M, Suzuki Y. Japan College of Rheumatology guideline for the use of methotrexate in patients with rheumatoid arthritis. *Mod Rheumatol* 2019;29(1):31-40.

28 Keino H, Watanabe T, Taki W, Nakashima C, Okada AA. Clinical features and visual outcomes of Japanese patients with scleritis. *Br J Ophthalmol* 2010;94(11):1459-1463.

29 Xu TT, Reynolds MM, Hodge DO, Smith WM. Epidemiology and clinical characteristics of episcleritis and scleritis in Olmsted County, Minnesota. *Am J Ophthalmol* 2020;217:317-324.

30 Nevares A, Raut R, Libman B, Hajj-Ali R. Noninfectious autoimmune scleritis: recognition, systemic associations, and therapy. *Curr Rheumatol Rep* 2020;22(4):11.

31 Sainz-de-la-Maza M, Molina N, Gonzalez-Gonzalez LA, Doctor PP, Tauber J, Foster CS. Scleritis associated with relapsing polychondritis. *Br J Ophthalmol* 2016;100(9):1290-1294.

32 Bielefeld P, Saadoun D, Héron E, Abad S, Devilliers H, Deschasse C, Trad S, Sène D, Kaplanski G, Sève P. Scleritis and systemic diseases: what should know the internist? *Rev Med Interne* 2018; 39(9):711-720.