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High-Dose Intravenous Pulse Methotrexate in Patients With Eosinophilic Fasciitis

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IMPORTANCE Eosinophilic fasciitis (EF) is a connective tissue disorder in which conventional treatment leads to disappointing results in a proportion of patients. Therefore, we investigated high-dose intravenous (IV) pulse methotrexate (MTX) as a treatment for EF.

OBJECTIVE To examine safety and effects of monthly high-dose IV pulse MTX in EF.

DESIGN, SETTING, AND PARTICIPANTS For this prospective single-arm study, we recruited 12 patients diagnosed with biopsy specimen–proven EF between 2006 and 2009 from the Department of Dermatology and Rheumatology at the Radboud University Medical Centre.

INTERVENTIONS Intravenous MTX (4 mg/kg) monthly for 5 months with folinic acid rescue 24 hours after MTX administration.

MAIN OUTCOMES AND MEASURES The primary outcome was improvement of the modified skin score at month 5 vs baseline. Secondary outcomes were durometry, range of motion, visual analog scale scores for disease activity, and 36-Item Short Form Survey health questionnaires.

RESULTS Overall, 12 patients (11 women between 37-69 years old) received a median (range) monthly dose of 288 (230-336) mg MTX. Median (range) modified skin score improved from 17.5 (8.0-24.0) at baseline to 8.5 (1.0-20.0) at month 5 (P = .001). Secondary outcome measures improved significantly, except for durometer scores and range of motion of the elbows. Adverse events included gastrointestinal symptoms (n = 9), mild stomatitis (n = 5), and alopecia (n = 4).

CONCLUSIONS AND RELEVANCE High-dose IV pulse MTX is a safe and effective treatment option in EF.

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Eosinophilic fasciitis (EF) is a rare connective tissue disorder of unknown etiopathogenesis. The disease is characterized by painful swelling and thickening of the skin and soft tissues of the extremities and less frequently the trunk.[1] Invalidating joint contractures are often reported in EF.[2,3] The diagnosis is established by histological examination of full thickness skin biopsy specimens containing subcutaneous fat and fascia.

Conventional treatment of EF consists of high-dose glucocorticoids combined with low-dose weekly methotrexate (MTX). However, disappointing results are described in a proportion of patients.[2,4-6] Therefore, additional therapeutic options are necessary. We observed increased efficacy of MTX exceeding the conventional dosages (maximum, 50 mg/week) at our outpatient clinic. Irrespective of these increased beneficial effects, clinical results were still not satisfactory enough. By using high-dose MTX we expected to induce a more pronounced effect on the involved skin. Furthermore, we hypothesized that intravenous (IV) administration would lead to fewer adverse effects. In this prospective study, we analyzed the safety and effect of monthly high-dose IV pulse MTX in patients with EF.

Methods

Patients and Study Design

Adult patients with biopsy specimen–proven progressive EF were recruited from the department of dermatology and rheu-

matology at the Radboud University Medical Centre between 2006 and 2009. Both MTX naive and nonnaive patients were eligible. A complete list of inclusion and exclusion criteria is displayed in eTable 1 in the Supplement. The IV pulse MTX was administered in a dose of 4 mg/kg every month for 5 months. Twenty-four hours after MTX administration, 5 mg folinic acid was administered every 6 hours, to a maximum of 25 mg for 1 day. The treatment regimen was based on an acute lymphoblastic leukemia protocol from the department of hematology. Glucocorticoids (maximum, 15 mg/d), nonsteroidal antiinflammatory drugs, analgesics, and antiemetics were allowed throughout the study. Patients could receive an additional 3 consecutive monthly IV MTX doses based upon the observation of a disease flare by the treating physician during follow-up without the study drug (glucocorticoids were continued during this follow-up). All patients gave their written consent. This study was registered (NCT00441961) and was approved by the Radboud University Medical Centre local ethical board (NL13046.091.06).

Outcome Measures

The primary outcome measure was the improvement in the modified skin score (mSS), according to Zachariae (eAppendix 1 in the Supplement),[7] at month 5 vs baseline. Additionally, skin hardness was measured by durometry (eAppendix 2 in the Supplement).[8] Joint contractures were monitored by measuring passive range of motion (RoM) of affected joints. Visual analog scale (VAS) scores for disease activity were scored by the physician and patient. Lastly, study participants filled out 36-Item Short Form Survey (SF-36) health questionnaires. Safety laboratory investigations were performed and adverse events (AE) registered.

Statistical Analysis

Descriptive statistics including median for continuous variables and percentages for categorical data were used. The Wilcoxon signed-rank test was performed to compare outcomes at baseline and month 5. The Mann-Whitney test was performed to compare outcomes between subgroups. A *P* value of .05 or less was regarded statistically significant. Statistical analyses were performed using SPSS version 22 (IBM).

Key Points

Question Is monthly high-dose intravenous pulse methotrexate a safe and effective treatment option for eosinophilic fasciitis (EF)?

Findings In this open prospective study that included 12 adults with eosinophilic fasciitis, the modified skin score improved significantly at month 5 compared with baseline. Adverse events were relatively mild and could be managed accordingly, and no serious adverse events were reported.

Meaning High-dose intravenous pulse methotrexate is a safe and effective treatment option in patients with EF.

Results

Demographics and Disease Characteristics

Twelve patients with EF (11 women) were enrolled. Baseline characteristics are shown in **Table 1**. Six patients were MTX-naive and 6 patients had received glucorticoids and MTX weekly prior to study participation (eTable 2 in the Supplement).

Effect of High-Dose MTX on Outcome Measures

Patients received a median (range) monthly dose of 288 (230-336) mg MTX. The primary outcome measure, median (range) mSS, improved from 17.5 (8.0-24.0) at baseline to 8.5 (1.0-20.0) at month 5 (*P* = .001) (**Figure**, A). No significant difference was observed between the change (Δ) mSS in MTX-naïve patients and nonnaive patients (*P* = .97) (Figure, B). In

Table 1. Baseline Characteristics of 12 Patients With Eosinophilic Fasciitis Enrolled for Study Participation

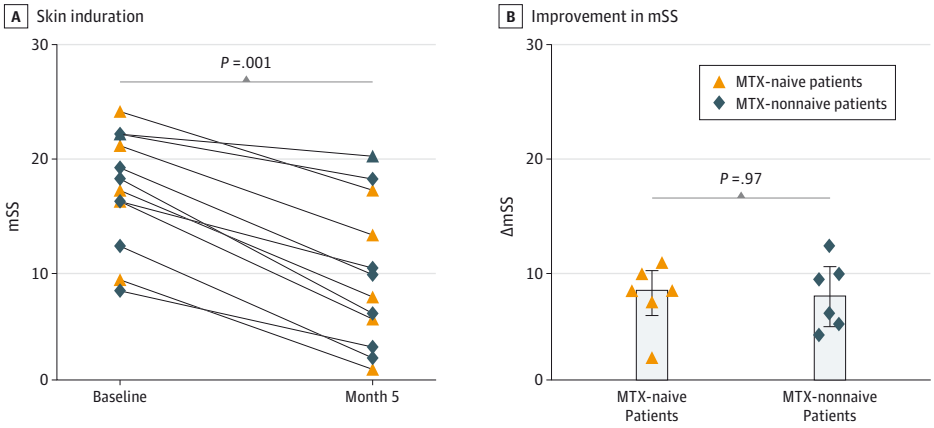
Patient No./Sex[a]	Disease Duration, mo	Treatment History		Cutaneous Involvement			Joint Involvement Contractures				Laboratory Results			
		MTX	GC	Trunk	Arms	Legs	Elbows	Wrists	Knees	Ankles	ANA[b]	ESR	CRP	Abs. EO Count
1/F	17	–	–	+	+	+	+	+	+	+	–	23	37	1.07
2/F	11	–	–	+	+	+	–	+	+	+	+	13	<5	0.38
3/M	2	–	–	+	+	+	–	+	+	+	–	3	17	0.53
4/F	12	–	–	–	+	+	–	+	–	+	–	6	12	0.12
5/F	10	–	–	+	+	+	–	+	+	+	–	2	15	1.13
6/F	8	–	+	+	+	+	+	–	+	+	–	9	8	0.03
7/F	130	+	+	+	+	+	+	+	+	+	–	5	<5	0.25
8/F	16	+	+	+	+	+	+	+	–	+	–	2	<5	0.20
9/F	83	+	+	+	+	+	+	+	+	+	–	52	48	0.17
10/F	18	+	+	+	+	+	+	–	+	–	+	6	<5	0.13
11/F	7	+	+	–	+	+	+	+	+	+	–	10	<5	0.20
12/F	15	+	+	+	+	+	–	–	+	+	–	9	10	0.06

Abbreviations: Abs. EO count, absolute eosinophil count (10^{9}/l); ANA, antinuclear antibodies; CRP, c-reactive protein (mg/l); ESR, erythrocyte sedimentation rate (mm/h); F, female; GC, glucocorticoids; M, male; MTX, methotrexate.

[a] Patients No. 1 to 6 are MTX naive and patients No. 7 to 12 have received MTX weekly (dose 15-50 mg) previous to trial participation. Patient No. 10 also received plaquenil and cyclosporine previous to study participation.

[b] Antinuclear antibodies, no systemic sclerosis specific antibodies by further testing were detected.

Figure. Skin Induration and Improvement Scored With Modified Skin Score



A, The primary outcome measure, skin induration, scored with modified skin score (mSS) at baseline and at month 5 for each patient. B, Improvement in mSS at month 5 compared with baseline (Δ mSS); Δ mSS for MTX-naive (left column) and MTX nonnaive (right column) are displayed by scatter plot and median. Comparison of median Δ mSS scores between the 2 subgroups showed no significant difference (P = .97). For 2 patients (Nos. 6 and 8) mSS scores were missing at month 5 and observations from month 4 were carried forward.

Table 2. Modified Skin Score and Secondary Outcome Measures at Baseline and at Month 5

Outcome Measure[a]	Participants Affected, No.	Median (Range)		P Value
		Baseline	Month 5	
Modified skin score	12	17.5 (8.0-24.0)	8.5 (1.0-20.0)	.001
Durometer score	12	44.0 (17.0-62.5)	44.0 (26.8-62.0)	.58
Range of motion				
Elbows	6	135.3° (122.0°-139.0°)	137.5° (126.0°-145.0°)	.69
Wrists	9	80.0° (45.0°-105.0°)	104.0° (54.0°-121.0°)	.004
Knees	9	92.0° (65.0°-122.0°)	127.0° (82.0°-152.0°)	.02
Ankle	11	29.0° (5.0°-56.0°)	45.0° (19.0°-75.0°)	.01
VAS				
Physician	12	78 (60-90)	47 (20-84)	.001
Patient	12	69 (40-90)	49 (5-81)	.001

Abbreviation: VAS, visual analog scale.

[a] For 2 patients (Nos. 6 and 8) modified skin score and durometer scores were missing at month 5, and observations from month 4 were carried forward.

addition, we observed no significant difference in Δ mSS between the patients whom received concomitant glucocorticoids (n = 8) and those who did not (n = 4) (P = .54). In 1 patient (No. 5), a temporary dose increase in glucocorticoids (to 30 mg) was required due to the severity of the disease.

The median durometer score did not improve (**Table 2**). The median (range) VAS for disease activity as judged by the physician decreased from 78 (60-90) to 47 (20-84) (P = .001). The median RoM of patients with affected wrists (n = 9), ankles (n = 11), and knees (n = 9) improved significantly with 24° (P = .004), 16° (P = .01) and 35° (P = .02), respectively (Table 2). The RoM of affected elbows did not improve (2. 2° increase; P = .67). Individual RoM measures are displayed in eFigure in the Supplement. Additionally, we observed a significant improvement in the domain (range) of physical functioning in the SF-36 (27.5 [5.0-65.0] to 47.5 [10.0-90.0]; P = .01). The VAS (range) for disease activity as judged by the patient decreased from 69 (40-90) to 49 (5-81) (P = .001).

Effect of Second High-Dose MTX Treatment Episode

In 6 patients, EF flared 2 to 5 months after completion of the primary treatment cycle. In these 6 patients, the treating physicians decided to restart treatment with 3 consecutive doses of IV pulsed MTX, and all 6 patients responded favorably again to the IV pulse MTX. The remaining 6 patients were not eligible for a second treatment cycle: in 2 patients, no disease progression was observed, another patient was regarded nonresponder, and 2 patients preferred to be treated conventionally with weekly low-dose MTX consecutive to the primary treatment episode. Lastly, despite a favorable response, 1 patient was withdrawn from the study because of adverse effects.

Safety

No serious AEs were reported during the study. However, 1 patient was withdrawn from the study due to elevated liver enzymes (alanine aminotransferase >2 times upper limit of normal). These enzymes normalized after study withdrawal. Nausea was reported in the majority of the patients (n = 9 [75%]). This was manageable with antiemetics in most patients, except for 1 patient; a 1-time dose reduction (to 3 mg/kg) was required to reduce nausea symptoms. Additional reported adverse effects were mild stomatitis (n = 5) and alopecia (n = 4).

Discussion

In this study, we present high-dose IV pulse MTX as a safe and effective treatment option in EF. The mSS decreased significantly. In contrast, durometer scores did not improve. This is probably owing to the fact that skin hardness in EF is often

present on skin overlying bony surfaces, such as the shins and lower arms. These locations are known, from localized scleroderma studies, to be less suitable for durometry.[8,9] The improvements in RoM we presented are clinically relevant because patients report a significant increase in physical functioning measured by the SF-36.

Regarding safety, we observed no serious adverse events and the treatment was relatively well tolerated. Observed adverse events, such as gastrointestinal symptoms and stomatitis could be managed accordingly. Interestingly, IV pulse MTX was effective in a subgroup of patients in whom disease progressed during conventional treatment. These results implicate that pulsed IV MTX might be an alternative treatment option in patients who fail on conventional treatment. Alternative treatments to weekly MTX have only been reported in case reports.[2,4,10-15] Comparing results of this study with observational studies with MTX in EF is difficult because these studies are retrospective and only report partial and complete remission rates without specifying outcomes in different disease parameters.[2,4-6] Some study-specific limitations including the variability in treatment history and the variability in concomitant glucocorticoids prescription might have influenced results. In addition, the lack of validated outcome measures for EF complicates the interpretation of the results. However, despite these limitations, this study provides evidence for an alternative treatment in EF.

Conclusions

High-dose monthly IV MTX is a safe and effective treatment option in patients with EF.

ARTICLE INFORMATION

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Author Contributions: Drs Mertens and Zweers had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Knaapen, Gerritsen, van den Hoogen, Creemers, de Jong.
Acquisition, analysis, or interpretation of data: Mertens, Zweers, Kievit, Gerritsen, Radstake, van den Hoogen, Creemers, de Jong.
Drafting of the manuscript: Mertens, Zweers, Gerritsen, van den Hoogen, Creemers, de Jong.
Critical revision of the manuscript for important intellectual content: Zweers, Kievit, Knaapen, Gerritsen, Radstake, van den Hoogen, Creemers, de Jong.
Statistical analysis: Mertens, Zweers, Kievit, Creemers, de Jong.
Administrative, technical, or material support: Zweers, Gerritsen, Creemers, de Jong.
Study supervision: Knaapen, Gerritsen, Radstake, Creemers, de Jong.
Treatment of patients, development of the protocol: Creemers.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Additional Contributions: We are indebted to the patients who participated in this study and their families.

REFERENCES

1. Lebeaux D, Sène D. Eosinophilic fasciitis (Shulman disease). *Best Pract Res Clin Rheumatol*. 2012;26(4):449-458.

2. Wright NA, Mazori DR, Patel M, Merola JF, Femia AN, Vleugels RA. Epidemiology and treatment of eosinophilic fasciitis: an analysis of 63 patients from 3 tertiary care centers. *JAMA Dermatol*. 2016;152(1):97-99.

3. Lakhanpal S, Ginsburg WW, Michet CJ, Doyle JA, Moore SB. Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. *Semin Arthritis Rheum*. 1988;17(4):221-231.

4. Lebeaux D, Francès C, Barete S, et al. Eosinophilic fasciitis (Shulman disease): new insights into the therapeutic management from a series of 34 patients. *Rheumatology (Oxford)*. 2012;51(3):557-561.

5. Berianu F, Cohen MD, Abril A, Ginsburg WW. Eosinophilic fasciitis: clinical characteristics and response to methotrexate. *Int J Rheum Dis*. 2015;18(1):91-98.

6. Kroft EB, Creemers MC, van den Hoogen FH, Boezeman JB, de Jong EM. Effectiveness, side-effects and period of remission after treatment with methotrexate in localized scleroderma and related sclerotic skin diseases: an inception cohort study. *Br J Dermatol*. 2009;160(5):1075-1082.

7. Zachariae H, Bjerring P, Halkier-Sørensen L, Heickendorff L, Søndergaard K. Skin scoring in systemic sclerosis: a modification—relations to subtypes and the aminoterminal propeptide of type III procollagen (PIIINP). *Acta Derm Venereol*. 1994;74(6):444-446.

8. Moon KW, Song R, Kim JH, Lee EY, Lee EB, Song YW. The correlation between durometer score and modified Rodnan skin score in systemic sclerosis. *Rheumatol Int*. 2012;32(8):2465-2470.

9. Seyger MM, van den Hoogen FH, de Boo T, de Jong EM. Reliability of two methods to assess morphea: skin scoring and the use of a durometer. *J Am Acad Dermatol*. 1997;37(5 Pt 1):793-796.

10. Alonso-Castro L, de las Heras E, Moreno C, et al. Eosinophilic fasciitis/generalized morphea overlap successfully treated with azathioprine. *Int J Dermatol*. 2014;53(11):1386-1388.

11. Antic M, Lautenschlager S, Itin PH. Eosinophilic fasciitis 30 years after - what do we really know? report of 11 patients and review of the literature. *Dermatology*. 2006;213(2):93-101.

12. Mendoza FA, Bai R, Kebede AG, Jimenez SA. Severe eosinophilic fasciitis: comparison of treatment with d-penicillamine plus corticosteroids vs corticosteroids alone. *Scand J Rheumatol*. 2015;45(2):129-134.

13. Bischoff L, Derk CT. Eosinophilic fasciitis: demographics, disease pattern and response to treatment: report of 12 cases and review of the literature. *Int J Dermatol*. 2008;47(1):29-35.

14. Espinoza F, Jorgensen C, Pers YM. Efficacy of tocilizumab in the treatment of eosinophilic fasciitis: report of one case. *Joint Bone Spine*. 2015;82(6):460-461.

15. Oza VS, Walsh R, North J, Berger TG, Murase JE. Treatment of eosinophilic fasciitis with sirolimus. *JAMA Dermatol*. 2016;152(4):488-490.