Methotrexate: an effective monotherapy for refractory generalized morphea

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Introduction: Morphea is an inflammatory skin disorder characterized by excessive collagen deposition. Although treatment algorithms for morphea subtypes have been suggested, no consistent recommendations are available. This study attempts to evaluate the clinical efficacy of methotrexate (MTX) as monotherapy in refractory generalized morphea.

Methods: It is a retrospective study, including 20 patients who had already been treated with various topical and systemic therapies with minimal clinical improvement. Patients received orally MTX at a dosage of 15 mg once weekly. Duration of the use, dosage of MTX, and adverse events were recorded. Clinical assessment of skin lesions was performed and documented.

Results: The mean disease duration was 27 months before the initiation of MTX treatment. After 12 months of therapy, very good response was achieved in 6 patients (30%), good response in 10 patients (50%), and fair response in 2 patients (10%), while 2 patients (10%) had failed treatment. Patients were followed up for a mean time interval of 21 months. No serious adverse event was recorded.

Conclusion: MTX has been already proved to be an effective and well-tolerated treatment in pediatric patients with morphea. The majority of the group of adult patients showed very good and good improvement when treated with MTX. Although this is an uncontrolled study, MTX monotherapy was considered a safe and effective treatment for the management of this specific clinical subset of morphea in adults.

Keywords: methotrexate, adults, generalized morphea
and ultraviolet A (PUVA) photochemotherapy, UVA1, cyclosporin, penicillamine, antimalarial drugs, and methotrexate (MTX).1–8

Although treatment algorithms for morphea subtypes have been suggested by Fett and Werth, there are still no consistent recommendations for the treatment of morphea based on the disease characteristics.9,10 This study attempts to assess the clinical efficacy and safety of MTX in refractory generalized morphea.

**Methods**

**Study population**

This was a retrospective study conducted between April 2010 and May 2015 at the Clinic for Autoimmune Dermatoses of “Andreas Sygros” Hospital, First Department of Skin and Venereal Diseases of National and Kapodistrian University of Athens Medical School, Greece.

Inclusion criteria were the following: 1) age 18 years; 2) clinical diagnosis of generalized plaque scleroderma defined as >4 indurated plaques >3 cm affecting at least 2 anatomic areas; 3) confirmation of clinical diagnosis by histologic and serologic examination; and 4) generalized morphea refractory to topical treatment (corticosteroids, calcineurin inhibitors, vitamin D analogs), PUVA, and oral corticosteroids. Patients who had additionally failed to other systemic treatments or combination treatment were not excluded from the study.

**Study procedures**

A total of 52 patients with generalized plaque scleroderma attended our Clinic for Autoimmune Dermatoses during this time period. Thirty-two patients demonstrated significant clinical improvement after being treated with any of the following treatments: topical corticosteroids, calcineurin inhibitors, vitamin D analogs, PUVA, and oral corticosteroids. The remaining 20 patients were included in this study.

The majority of patients were female (17 patients). The average age at the onset of the disease was 50 years. The frequencies of concomitant diseases from patients’ medical history were the following: coronary artery disease in 7 patients (35%), diabetes in 4 patients (20%), and elevated cholesterol in 5 patients (25%). Nine patients (45%) were smokers. Family history of autoimmune diseases was identified in 3 patients (15%). Six patients (30%) described symptoms of Raynaud’s phenomenon.

All patients had minimal clinical improvement when treated with the above mentioned topical treatments. Furthermore, all of them had failed PUVA (although high-dose UVA1 light is likely the most effective ultraviolet light therapy for morphea, it was not available in our hospital). Subsequently, they had been refractory to systemic treatment with oral corticosteroids. Each treatment had been administered as monotherapy. A total of 2, 3, and 2 patients had no response when later being treated with penicillamine, hydroxychloroquine, and combination of oral corticosteroids and topical calcineurin inhibitors, respectively.

Clinical characteristics of patients were recorded comprising the disease duration, past treatments for morphea, and extracutaneous manifestations of the disease, while family history of autoimmune diseases was also indicated. Clinical diagnosis was confirmed by skin biopsy and histologic examination. Laboratory examinations included antinuclear antibodies (ANAs); anti-topoisomerase I antibodies (anti-Scl-70); complement fractions (C3 and C4); and anti-Pm/Scl, anti-Sm, anti-U1-RNP, anti-Ro/SSA, and anti-La/SSB antibodies.

Standard screening prior to treatment initiation with MTX consisted of a full blood count, liver biochemistry, serum urea, and creatinine. These tests were performed twice weekly for the first 3 months of treatment, four times weekly during the second 3 months of treatment, and thereafter thrice monthly in the case of stable dose and no toxicity.11 Serology tests for Hepatitis B (HBV) and Hepatitis C (HCV) and tuberculosis testing were considered for high-risk patients. A chest X-ray was appropriate for patients with lung disease such as asthma, bronchitis, or smoker’s cough. Pregnancy test was performed in sexually active women of childbearing age. A reliable form of birth control was critical throughout the course of treatment.

Patients received MTX orally at a dosage of 15 mg once weekly. Folic acid supplementation was administered 24 hours before and after the intake of MTX. The overall disease activity and function was assessed every 3 months. The duration of the use and dosage of MTX and adverse events were recorded.

Treatment was ceased in cases of very good improvement, lack of improvement, progressive disease, or not manageable adverse events based on the judgment of our clinical team.

Fourteen out of 20 patients (70%) received MTX as a sole systemic treatment, whereas the other ones were administered a combination of oral MTX and/or topical emollients.

Clinical assessment of skin lesions was performed based on 3 criteria: erythema, skin thickness/induration, and size of the lesion. This evaluation of the outcomes was represented on a mannequin and documented in patients’ medical files. A Physician’s Global Assessment (PGA) scale was also used to evaluate the efficacy of the treatment with MTX after 6, 9, and 12 months of therapy based on the improvement of the
above mentioned 3 criteria. Treatment failure was defined as no improvement in any of the 3 criteria and/or appearance of the disease activity/function, that is, worsening of the sclerosis, presence of lilac ring, increase of lesion size, and presence of new lesions within previous visit. Very good response was defined as improvement in all 3 criteria, good as improvement in 2 out of 3 criteria, while fair response as improvement in 1 out of 3 criteria. Moreover, all patients were asked to complete a Dermatology Life Quality Index (DLQI) questionnaire to evaluate the impact of the disease on the patient’s quality of life.12

**Compliance with ethics guidelines**

This study was conducted in the Dermatology Department of Andreas Sygros Hospital of Cutaneous and Venereal Diseases in Athens. The study protocol was approved by the ethics committee of the hospital, and written informed consent was obtained from all patients.

**Results**

The patients in this study had a mean disease duration of 27 months before the initiation of MTX treatment. Clinically, most of the patients in general started to show signs of experienced marked or moderate improvement within the first 3 months of therapy and continued to improve throughout the next months. A significant improvement in clinical manifestation was reflected in scoring systems including DLQI score (Table 1). According to PGA, 3 months on treatment, patients had very good, good, and fair response, while only 2 failed treatment; thus, treatment was discontinued in both cases (Table 2). After 12 months of therapy, very good response was achieved in 6 patients (30%) and good response in 10 patients (50%). These patients were followed up for a mean time interval of 21 months. During the follow-up period, no new skin lesions of generalized morphea appeared, and no exacerbation of the disease was observed.

No serious adverse event was recorded in the patient group of this study. Nausea and abdominal pain were observed in 4 patients (20%). Only 1 patient developed acute elevation of liver biochemistry, which was normalized after reducing dosage of MTX to 10 mg once weekly for 2 consecutive weeks. Treatment discontinuation was not required in any of the above mentioned cases.

Seven patients (35%) were ANA positive, 1 patient (5%) was anti-Scl-70 positive, while C3 and C4 were within normal range in all patients. Anti-Pm/Scl, anti-Sm, anti-U1-RNP, anti-Ro/SSA, and anti-La/SSB antibodies were not detected in any of the patients.

**Discussion**

Morphea with >4 lesions affecting at least 2 anatomic areas is usually limited to the skin and subcutaneous tissue and

**Table 1 Patients’ demographic characteristics and DLQI scores before and at the end of the treatment with MTX**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Disease duration (months)</th>
<th>Coronary artery disease</th>
<th>Diabetes mellitus</th>
<th>Smoking history</th>
<th>Family history of autoimmune disease</th>
<th>DLQI score Baseline/end of treatment (points)</th>
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<tr>
<td>1</td>
<td>F</td>
<td>47</td>
<td>8</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<td>11/5</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>44</td>
<td>14</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>12/7</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>54</td>
<td>12</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
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<tr>
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<td>51</td>
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<tr>
<td>5</td>
<td>F</td>
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<td>N</td>
<td>12/3</td>
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<tr>
<td>6</td>
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<td>9</td>
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<tr>
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<td>52</td>
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<td>M</td>
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<td>Y</td>
<td>N</td>
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<td>N</td>
<td>7/2</td>
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</table>

*Abbreviations: DLQI, Dermatology Life Quality Index; MTX, methotrexate; F, female; M, male; Y, yes; N, no.*
Table 2 A Physician’s Global Assessment (PGA) scale was used to evaluate the efficacy of the treatment with MTX after 6, 9, and 12 months of therapy

<table>
<thead>
<tr>
<th>PGA</th>
<th>Number of patients after 6 months of therapy</th>
<th>Number of patients after 9 months of therapy</th>
<th>Number of patients after 12 months of therapy</th>
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<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>2 (10)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Fair response</td>
<td>5 (25)</td>
<td>2 (10)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Good response</td>
<td>9 (45)</td>
<td>8 (40)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>Very good response</td>
<td>4 (20)</td>
<td>8 (40)</td>
<td>6 (30)</td>
</tr>
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Abbreviation: MTX, methotrexate.

Table 2

MTX has been studied as a treatment option for both morphea and systemic sclerosis. It is a folic acid antagonist that closely resembles folic acid in structure. It inhibits folate-dependent enzymes, such as dihydrofolate reductase. This enzyme is involved in pyrimidine (DNA) synthesis. Inhibition of this enzyme leads to depletion of tetrahydrofolates, which are essential for the synthesis of DNA, RNA, and protein. Advantages of treatment with MTX include a weekly dosage schedule, low cost, and a relatively safe profile. Whereas adverse events like nausea, vomiting, fatigue, and mucositis are common, they are rarely life-threatening. While pulmonary toxicity is very rare, hepatic and toxicities toxicity are common with MTX but not usually severe, particularly when the dose is low and can be managed with dose reduction as needed. Consequently, frequent blood monitoring is required.

Although this is an uncontrolled study, there do appear to be encouraging results, since the majority of the patient group (80%) of this study showed good and very good response after 12 months of MTX treatment. Only 2 patients had to discontinue treatment due to no response to therapy or worsening of their clinical condition.

According to literature, MTX has been proved to be an effective and well-tolerated treatment for achieving disease remission in pediatric patients with LS. However, few studies have been conducted in adult population. In a cohort study, Kroft et al have demonstrated the efficacy of MTX for various sclerotic skin diseases (LS, eosinophilic fasciitis, and pseudoscleroderma) in adult patients. In another study, improvement was observed in adult patients with severe morphea treated with pulsed intravenous corticosteroids plus MTX. van den Hoogen et al have shown that MTX therapy in systemic sclerosis resulted in reduction of skin thickness and improvement in general well-being. Similar findings have been reported by Pope et al. In addition, a recent retrospective chart review of adult patients with morphea treated with MTX showed that younger age at treatment initiation was associated with higher rates of disease remission, suggesting that early treatment should be preferred in morphea.

The mechanism of action of MTX is not fully understood. MTX is considered to ameliorate skin fibrosis. This may be attributed to its anti-inflammatory effect or to a possible direct effect on the skin fibroblasts. Both Seyger et al in an adult LS series and van den Hoogen et al in an adult systemic sclerosis trial suggested that MTX may have an anti-fibrotic action. A possible mechanism of MTX in modifying morphea is by interfering with cytokine expression. Decreased levels of circulating soluble interleukin-2 receptors and decreased serum levels of interleukin-6 and interleukin-8 after MTX treatment have been reported both in juvenile and in adult rheumatoid arthritis, while increased levels of the above mentioned cytokines have been related to an active phase in morphea. In addition, a recent study showed that suppression of the JAK/STAT pathway is likely to be the principal anti-inflammatory and immunosuppressive mechanism-of-action of low-dose MTX.

Conclusion

MTX was considered a safe strategy for the management of this specific clinical subset of morphea. The overall tolerability of the treatment was high, and the adverse events observed were mild and reversible. Nevertheless, this is an uncontrolled study of a disease with a tendency to spontaneous improvement so it is difficult to be certain that improvement is due to MTX.

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Disclosure

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References