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CASE REPORT

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The use of methotrexate in the treatment of selected autoimmune connective tissue diseases — our own experience and review of the literature data

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ABSTRACT

Methotrexate (MTX) belongs to the most commonly used immunosuppressants in dermatology. Correct classification of the patient, taking into account possible contraindications may minimize the risk of adverse effects of MTX, while the emergence of new forms for applications of MTX — subcutaneous prefilled syringes — significantly improved bioavailability compared to oral treatment and allowed to increase the efficacy and safety of the treatment. We present our experience with the use of subcutaneous MTX in the treatment of chronic cutaneous lupus erythematosus (Discoid Lupus Erythematosus, DLE) and in generalized as well as deep forms of morphea. In addition, we reviewed the literature and current guidelines regarding treatment of both diseases.

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Key words: methotrxate, autoimmune connective tissue diseases, morphea, dyscoid lupus erthematosus, DLE

INTRODUCTION

Methotrexate (MTX), synthesized in the '50s of the last century as an anticancer drug with antiproliferative action, is now the most commonly used immunosuppressant in dermatology [1]. Application of low, nononcological doses revealed its anti-inflammatory properties, including effects on cytokines involved in the pathogenesis of diseases of the immune etiology. It is known that MTX reduces the synthesis of IL-1, IL-6, TNF-α, IFN-γ, GM-CSF and inhibits chemotaxis of neutrophils into the dermis [1–3].

Its use in many skin diseases, particularly in severe psoriasis and psoriatic arthritis, familiarized physicians with its pharmacokinetic properties and allowed a rational dosing and effective monitoring of the therapy [4]. Correct classification of the patient, taking into account possible contraindications may minimize the risk of adverse effects of MTX. The emergence of new forms for applications of MTX — subcutaneous prefilled syringes — significantly improved bioavailability compared to oral treatment and allowed to increase the efficacy and safety of treatment. Another important, from a clinical point of view, advantage for subcutaneously administrated MTX is the reduction of the possible undesirable effects of the gastrointestinal tract [5–7].

As mentioned above, psoriasis is the most common skin disease where MTX is used. Other dermatological diseases treated with MTX are, among other, pityriasis rubra pilaris, sarcoidosis, skin lymphomas, lichen planus and atopic dermatitis [1, 8–11]. In the group of autoimmune skin diseases positive therapeutic effect of the drug was observed in bullous pemphigoid and connective tissue diseases, like dermatomyositis, cutaneous lupus erythematosus (CLE) and localized scleroderma (morphea) [11–27]. Unfortunately, according to CLE and morphea there are no randomized trials using MTX, and most of the literature is based on the analysis of case series [16–27]. However, in accordance with the therapeutic recommendations for morphea, MTX is a second-line drug after phototherapy in a generalized form of the disease and the first-line drug in the linear form [28, 29]. In regards of CLE MTX should be considered as

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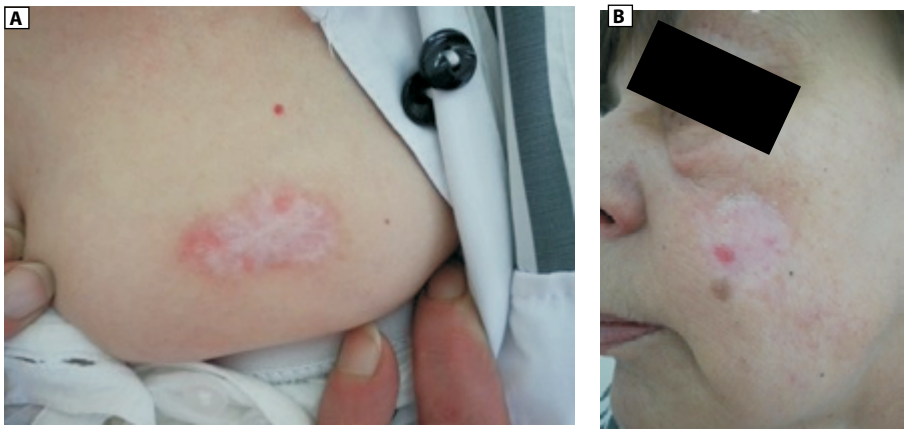

Figure 1A. Lesions on the skin of the left breast in female patient with DLE before treatment; **B**. DLE skin lesions within the left cheek before treatment

a therapeutic option in the case of ineffectiveness of antimalarial drugs [30].

Below we present our experience with the use of subcutaneous MTX in the treatment of DLE and in generalized as well as deep forms of morphea. In addition, we present a review of the literature and current guidelines regarding the treatment of both diseases.

CASE 1

51-year-old female patient came to the Outpatient Clinic of Department of Dermatology at University of Medical Sciences due to persistent for about 3 years and intensifying in the summer disseminated skin lesions localized on the skin of scalp, left breast and face. Additionally, history revealed psoriasis vulgaris from the age of 16, with low severity (Body Surface Area, BSA < 10%, Psoriasis Area Severity Index, PASI < 10%) within predilection sites.

On the scalp around the top of the head scarring alopecia and erythematous and scaly lesions were observed, while within the skin of the left breast intensively 3 cm erythematous lesion with hyperkeratosis was detected (Fig. 1A). Within the left cheek an erythematous and infiltrative lesions in the center was revealed (Fig. 1B). From lesional skin of left breast biopsy was taken for histopathological examination, yielding an image typical of DLE. The titer of antinuclear antibody (ANA) was 1:160 (the specificity of the these antibody was not demonstrated). A series of additional tests excluded the diagnosis of systemic lupus erythematosus (according to the criteria of the Systemic Lupus Collaborating Clinics, SLICC [31]).

Initially, chloroquine (CHQ) at a dose of 250 mg daily was implemented (after ophthalmological consultation and the assessment of contraindications). Topically applied steroids with medium and high potency, and later also 0.1% tacrolimus in ointment were introduced. Photoprotection (SPF 50+) and avoidance of exposure to UV radiation was also recommended. During this therapeutic regimen transient dermatological improvement after approximately 3 months was observed, however, in next subsequent weeks no further improvement of DLE, was found, but also psoriatic lesions were exacerbated.

After qualifying tests it was decided to start MTX therapy and discontinuation of CHQ. At the beginning, test dose of MTX (5 mg/week orally), while in the next week, after the normal laboratory results, therapeutic dose of MTX 15 mg/week was recommended. Additionally, supplementation with folic acid at a dose of 15 mg once after 24 hours from administration of MTX was implemented. In the day of taking the test as well as therapeutic dose patient reported nausea, lack of appetite, dyspepsia. These symptoms recurred during 2 consecutive drug intakes, causing the reluctance of patients to continue the therapy of MTX. Possible side effects of MTX were discussed with the patient and transition to subcutaneous therapy (s.c.) at a dose of 15/mg per week was offered to our patient.

During MTX administrated s.c. the patient did not complain to the troubling side effects of the gastrointestinal tract. Monitoring MTX therapy was carried out according to the approved scheme, and found no adverse effects. During subsequent visits a gradual improvement of dermatological lesions in the type of DLE and psoriasis was noticed (Fig. 2A i B). MTX therapy was continued for a one year.

CASE 2

A forty-seven-year old male patient was consulted in the Outpatient Clinic because of the disseminated skin lesions localized on the skin of the upper and lower extremities, which appeared a few weeks before the visit. The classic morphea plaques with induration in the center in number of 9, surrounded by lilac ring on the skin of both forearms (Fig. 3A) and lower limbs were detected. The patient was diagnosed a few weeks earlier with glaucoma and remained under the ophthalmological care.

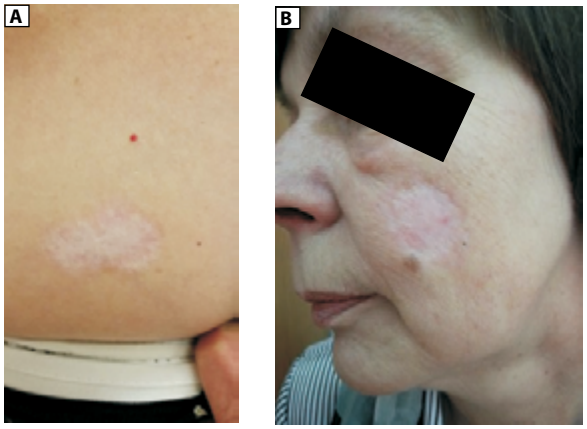

Figure 2A. Dermatological improvement within the left breast in female patient with DLE after approximately 4 months of MTX s.c. therapy; **B**. Resolution of erythematous and infiltrative lesions on the skin of the left breast in female patient with DLE after approximately 4 months of MTX s.c. therapy

Due to the contraindications to the steroid therapy (glaucoma) and the fear of steroid treatment, MTX orally — according to the scheme described for patient 1 — was implemented. For a period of 16 weeks, at a therapeutic dose of 15 mg/week no dermatological improvement was observed. It was decided to change the route of administration — to pre-filled syringes for s.c. applications at a dose 20 mg/week. After 4 weeks of the implementation of MTX s.c. we could observe disapperance of skin lesions within forearms (Fig. 3B) as well as softening of the skin and lack of liliac ring within the lesions of lower legs. During subsequent visits (after 8 weeks of inclusion MTX) we detected complete resolution of all the plaques within the skin of the forearm and the appearance of hyperpigmented patches within lower limbs. After 6 months of implementation of MTX, the patient stop the use of the drug without consulting the doctor. In the following weeks, there was a recurrence of skin lesions mainly on the skin of the forearm. Again, MTX s.c. was introduced, once again improving the dermatological status.

CASE 3

A sixteen-year-old female patient was referred by pediatrician, rheumatologist to our Outpatient Clinic of Department of Dermatology at University of Medical Sciences because of skin lesions localized on the skin of the lower legs. The first skin lesions, described by the girl and her parents as an erythematous patches, were not accompanied by additional symptoms. The lesions emerged a few weeks before the visit and showed rapid progression. On the first visit induration with pronounced erythematous infiltration at the periphery within the left leg was visible (Fig. 4A), while within right ankle and the proximal right leg marked loss of subcutaneous tissue and muscle, without the accompanying inflammation was detected (Fig. 4B). In addition, history revealed irritable bowel syndrome for approximately one year, controlled by trimebutin. Histological examination confirmed diagnosis of morphea profunda.

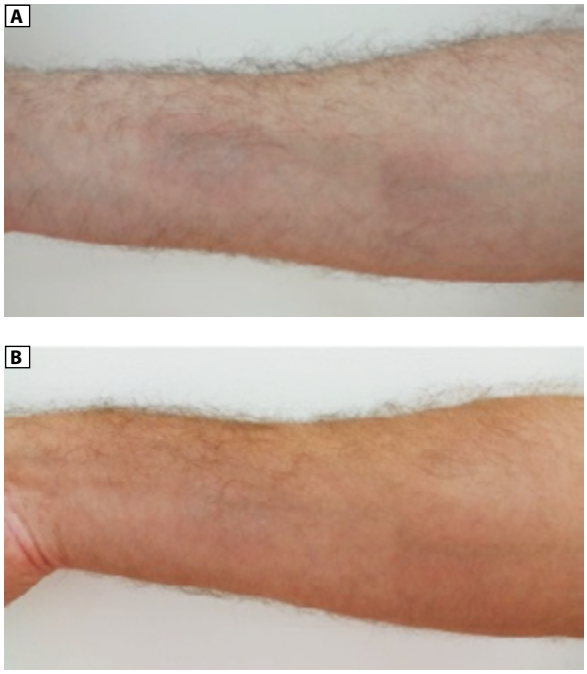

Figure 3A. Characteristic active lesions in morphea within the right forearm before treatment; **B**. The complete resolution of skin lesions in the type of morphea within the right forearm after 16 weeks of MTX therapy and 4 weeks of MTX s.c. therapy

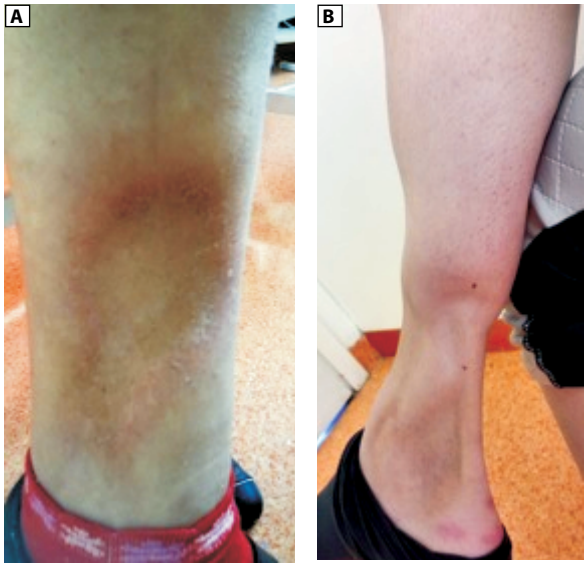

Figure 4A. Lower leg region in female patient with morphea profunda before treatment; **B**. Right ankle region and the proximal part of the right lower leg with the loss of subcutaneous tissue and muscles in morphea before treatment

Two weeks before the visit in our clinic the patient was hospitalized in the rheumatologic ward where glucocor-

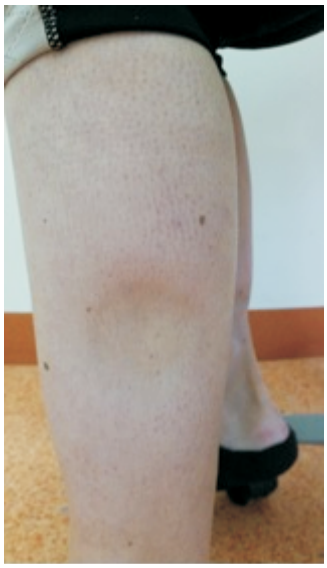

Figure 5. Dermatological improvement within the left lower leg after 4 months of the combined therapy (MTX and glucocorticoids therapy)

ticosteoids in intravenous pulses (methylprednizolon 3 × 500 mg in 3 courses with 1 month brake) were administrated followed by oral steroid (methylprednisolone in doses gradually reduced) in combination with MTX. Due to the often reported by parents and the girl dyspeptic symptoms, after the qualification — MTX s.c. at a dose of 15 mg/week was started.

After 3 months from the introduction of MTX and at a daily dose of methylprednisolone 8 mg orally, we could observe disappearance of erythema, decreased in skin induration and reduction of the area of the left leg affected by the disease process (Fig. 5). In the skin of the right leg, there was no further spread of atrophic changes. MTX s.c therapy was continued for a period of 12 months to complete the resolution of lesions within the left lower leg.

DISCUSSION

Numerous scientific reports indicate that MTX is a good and safe therapeutic option in the treatment of many skin diseases, especially if there are concerns about the side effects of the long-term steroid therapy or if internist contraindications to introduce steroids exist [1]. An important element, often hindering the treatment of skin diseases, is widespread in society corticophobia. That is why, the use of drugs from other groups, including herein discussed MTX, may be applied.

The first mentions of MTX therapy in lupus erythematosus are from 1965 and are related to its systemic form [32]. Whereas the use of MTX in CLE, as it was mentioned before, is based mostly on the analyses of case series, which mainly come from the 90s of the last century [14–21]. Boehm analyzed 12 patients with CLE, 4 with DLE, 6 with subacute cutaneous lupus erythematosus (SCLE), 1 with deep form and 1 patient with the chilblain lupus erythematosus. MTX was used both orally as well as intravenously with complete remission of skin lesions in 6 patients, and improvement in the subsequent 4 [21]. Another study using oral and intravenous administration MTX describes retrospectively 43 CLE patients in whom satisfactory improvement of dermatological status was observed in majority of patients (42 patients), particularly in SCLE and DLE, together with a good tolerance of a therapy [17]. One of the recent reports of the same researchers, regards to the use of MTX s.c in a group of 15 patients (2 with DLE), who previously received the drug intravenously. According to Huber et al. in therapy of CLE s.c. administration of MTX is as effective as intravenous one [33].

Most currently used treatment protocol for CLE includes both topical (including UV protection) and systemic drugs. Typically, the control of disease symptoms by topical steroids, calcineurin inhibitors is insufficient and requires systemic treatment. The first-line systemic drugs in CLE are antimalarial drugs (CHQ, hydroxychloroquine). In the absence of the effects of these drugs or if there are contraindications to them, second-line drug, which is MTX, should be added [30, 34].

The first case presented herein — patients with disseminated DLE — MTX therapy was introduced due to the lack of the effect of antimalarial and topical drugs. Moreover, CHQ belongs to the drugs aggravating psoriasis and observed by our patient worsening of psoriasis (still BSA < 10%, PASI < 10%) was significant. Coexistence of psoriasis and lupus erythematosus, according to the literature data, may affect 1% of patients and is a major therapeutic challenge. It is due to a well known potential aggravating effect of antimalarial and the systemic glucocorticoids therapy in psoriasis (with a possible development of pustular psoriasis), from the second – anti TNF-α drugs used to treat psoriasis — may exacerbate lupus [35].

MTX therapy administrated s.c. in our patient with DLE was introduced due to the symptoms of gastrointestinal intolerance. Nausea and vomiting are very common side effect of the treatment with oral MTX and may affect 20–43% of patients [36]. The gastrointestinal epithelium, in addition to bone marrow cells, is the most vulnerable tissue in regards of possible side effects of this drug. Although the symptoms are transient, they are usually hardly accepted by the patient and in the case of our patient they appeared during next 3 administrations of the drug (at a test dose and the next two therapeutic doses) [36]. After the conversion of MTX into its s.c. form, gastrointestinal symptoms were no longer reported by the patient.

The next two presented cases treated with MTX s.c. concern morphea, both disseminated form and less fre-

quently observed deep type. According to the therapeutic guidelines in disseminated morphea, MTX is recommended for the use in conjunction with systemic steroid therapy [28, 29]. In second patient coexisting glaucoma was reported and he was afraid of steroid therapy (mainly of weight gain and osteoporosis). Thus MTX orally 15 mg/week was introduced initially, but within 16 weeks of treatment there was no dermatological improvement. Due to the fact that the absorption of orally administered MTX increases in a linear way to 15mg dose and at higher doses is absorbed less, it was decided to increase the dose to 20 mg/week and to convert the route of administration into s.c. Research shows that MTX s.c. has greater bioavailability at doses greater than 15 mg than the corresponding oral dose. In addition, MTX administered s.c. has no first-pass effect and connecting to the longer poliglutamine chain exerts potent anti-inflammatory activity [5–7].

Very good therapeutic effect of MTX s.c. for the treatment of localized scleroderma was also observed in the last presented patient, where due to the limb involvement, the acquisition of subcutaneous tissue and a significant risk of permanent impairment of the limb function, therapy was also conducted with the participation of the high doses glucocorticosteroids. In this case, in order to obtain a good effect — we introduced MTX s.c. from the beginning. In addition, the patient and her parents were afraid of gastric symptoms of MTX administered orally, which with the systemic steroids and concomitant irritable bowel syndrome could be worse.

Single prospective studies and retrospective reports based on cases series, including children, confirm the efficacy of the combined therapy in morphea: systemic steroids (usually high-dose therapy pulse) and MTX (0.3–0.4 mg/kg/week in children and 15–25 mg weekly for an adult) [22–27, 29]. One recent retrospective study shows 107 patients with morphea treated with MTX (including 2 patients treated with MTX s.c. and 37 treated with combined therapy). From this group — 25% of patients after one year discontinued the treatment with MTX due to remission, and 62% after two years [37]. The median time to discontinuation of MTX due to disease remission was 87 weeks. The researchers identified possible predictors for disease remission like younger age at MTX initiation, absence of other autoimmune diseases and absence of deep morphea. Moreover, they observed that young patients often obtain remission after MTX, which can be associated with the existence of a number of co-morbidities in elderly patients. Additionally, they showed that patients with a longer delay according the inclusion therapy with MTX - had worse therapeutic effects, this may suggest the need for rapid introduction of therapy, just as it is, for example, in rheumatoid arthritis [37, 38].

In summary, MTX is the drug recommended both for the treatment of lupus erythematosus and morphea. Compliance with the general guidelines for the use of this drug (proper selection of patients, periodic laboratory tests, pregnancy tests, the use of adequate doses and the optimal route of administration, folic acid supplementation) enables long-term therapy [4, 36]. MTX s.c. can be used at home by the patient himself,is characterized by slight tenderness during injection and rarely causes adverse events.

No conflict of interest.

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