
Use of methotrexate in patients with scleroderma and mixed connective tissue disease

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ABSTRACT

Systemic sclerosis (scleroderma, SSc) and mixed connective tissue disease (MCTD) are chronic autoimmune diseases characterised by a broad spectrum of clinical manifestations including different forms of musculoskeletal involvement, skin and vascular changes, as well as internal organ complications. Clinical course and outcomes might vary from mild forms with good clinical prognosis to severe rapidly progressive life-threatening diseases. At present, immunosuppressive therapies are considered a cornerstone in the treatment of MCTD, and are frequently used in clinical practice in SSc despite limited evidence from clinical trials. The aim of the present review is to discuss available data concerning efficacy of methotrexate therapy in SSc and MCTD.

Introduction

Systemic sclerosis (scleroderma, SSc) and mixed connective tissue disease (MCTD) are autoimmune diseases characterised by a broad spectrum of clinical manifestations including different forms of musculoskeletal involvement, skin changes, as well as internal organ complications (1, 2). The natural history of the disease and clinical outcome are highly variable in both SSc and MCTD. Some patients have a mild, slowly progressive or self-limited disease, whereas others develop major organ involvement that requires aggressive treatment. No universal disease-modifying drugs are available for SSc and MCTD, and it is generally agreed that treatment depends on each patient's clinical involvement (organ-targeted therapy). Clinical heterogeneity is one of the main obstacles in performing clinical trials in SSc and MCTD and for these reasons only a few therapies have proved effective in disease-specific randomised clinical

trials. Methotrexate (MTX), which proved effective in rheumatoid arthritis (3 and reviewed in other chapters of this issue), is also considered an option in treating SSc and MCTD. In the present review we discuss the available evidence concerning usage of MTX in SSc and MCTD.

Use of methotrexate in systemic sclerosis

Background

Systemic sclerosis (scleroderma, SSc) is a multisystem connective tissue disease characterised by widespread vasculopathy and profound fibrosis of the skin and internal organs. Involvement of internal organs, such as the lungs, heart, gastrointestinal tract and/or the kidneys results in high morbidity and mortality in SSc patients. At present, pulmonary complications including interstitial lung disease (pulmonary fibrosis) and pulmonary arterial hypertension are the leading causes of death accounting together for almost 60% of disease-related mortality in SSc patients (4).

The natural clinical course of disease might vary. There are two major forms of the disease: limited cutaneous SSc (lSSc) and diffuse cutaneous SSc (dSSc), which differ with respect to extent and progression of skin thickening, but also with respect to a pattern of internal organ involvement and life expectancy (5).

In patients with lSSc skin changes are limited to face and distal parts of the extremities, the disease progress is slow and severe internal organ involvement (usually interstitial lung disease or pulmonary arterial hypertension) develop at later stages, often after several years from first symptoms attributable to SSc. In patients with dSSc skin thickening is much more extensive spreading from the distal parts to the arms, thighs and the trunk, the pace of skin changes is much more rapid, especially in the first

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years of the disease, and severe internal organ involvement (usually interstitial lung disease, renal failure, heart or gastrointestinal involvement) might develop early.

Although destructive arthritis is uncommon in SSc, musculoskeletal involvement is frequent in SSc and includes joint pain, joint contractures due to skin changes, non-erosive arthritis, tendon friction rub, myopathy and myositis (1). SSc can also occur co-existing with other fully developed autoimmune diseases such as rheumatoid arthritis or polymyositis; this situation is often referred to as overlap syndromes (2).

Factors triggering SSc are not known. Although the pathogenesis of SSc is not fully clarified, clinical and experimental evidence indicates that autoimmunity, vascular injury and excessive production of connective tissue play key roles in the development and progression of the disease (6). Understanding of the processes involved in SSc pathogenesis led to design of treatment strategies. Accordingly, recognition of the presence of autoimmune phenomenon in SSc, such as the presence of autoantibodies, associations between specific autoantibodies and particular disease patterns/outcomes and the presence of perivascular inflammatory mononuclear cell infiltration in the skin and internal organs in early diffuse rapidly progressive SSc, have led to the usage of immunosuppressive therapies in SSc.

Clinical studies of methotrexate in SSc

So far, the results of two multicentre randomised clinical trials investigating the efficacy and safety of MTX in SSc have been published (7, 8).

The first trial involved 29 SSc patients with early disease, defined as disease duration shorter than 3 years from first signs of skin thickening. Patients with longer disease duration were also included if they had experienced progression of skin thickening, persistent digital ulcerations, or deterioration in pulmonary function during the last 6 months. Seventeen patients received MTX at a dose of 15mg/week given as intramuscular injections, while the remaining 12 received injections with placebo (7).

Patients were evaluated in a double-blind manner and clinical response to treatment was defined as improvement by at least 30% in total skin score, by at least 15% in DLCO or by at least 50% in visual analogue scale (VAS) of well being, provided that such improvement was not accompanied by persisting digital ulcerations or decrease in DLCO by at least 15%. Twenty-five out of 29 patients completed 24 weeks of treatment. In the completers, favourable response to treatment/clinical improvement was seen more frequently in patients receiving MTX (eight out of 15=53%) when compared with the placebo-treated group (one out of ten=10%, $p=0.03$). The favourable response to treatment was due to skin score improvement in 3 patients, VAS improvement in 4 patients, and both skin and VAS improvement in 1 patient. An intent-to-treat analysis of single variables revealed a trend towards improvement of skin score and creatinine clearance in the MTX group at week 24 ($p=0.06$ and $p=0.07$ versus placebo, respectively).

An extension study of another 24 weeks, during which MTX was given at 15mg/week in 9 MTX responders and in 9 patients from the placebo group, or increased up to 25mg/week in 6 MTX non-responders, revealed improvement in skin score and/or VAS in 15 out of 23 (68%) patients who completed 48 weeks. No significant differences in clinical variables could, however, be identified at week 48 when compared with baseline values. Laboratory evaluation revealed significant decrease in haemoglobin, white blood cells, platelets and IgG levels, when compared with baseline values.

Six patients (21%) withdrew from the study during 48 weeks: four due to SSc-related causes (death or renal crisis), 1 due to sudden death and 1 due to side effects of treatment (persistent, severe headache after each injection). One patient, who subsequently died due to severe interstitial lung disease, had experienced transient pancytopenia, which resolved after MTX withdrawal. Transient elevation of liver enzymes was observed in 6 patients receiving MTX. Liver enzymes normalised after

temporary MTX withdrawal and did not increase after resuming MTX.

Another larger multicenter double-blind randomised trial included 71 patients with early dSSc of less than 3 years duration, 35 of whom received MTX (orally 15mg-17.5mg/d) and 36 received placebo (8). After 12 months, an intent-to-treat analysis showed improvement in skin scores in the MTX group ($p<0.04$ for the University of California Los Angeles (UCLA) skin score and $p<0.09$ for the modified Rodnan skin score (mRSS)) versus placebo. The mean changes in skin scores were rather small (-1.2 for UCLA and -4.3 for mRSS in the MTX group compared with 1.2 and 1.8 in the placebo group, respectively, $p<0.05$ for both UCLA and mRSS), and the difference in the UCLA score lost its significance after adjustment for use of steroids and sex differences ($p<0.07$). MTX appeared also to better preserve diffusing capacity of the lungs (DLCO) ($p<0.03$ for between group comparison at 12 months), however, the mean DLCO changes were small and did not differ significantly (-3.7% in MTX group vs. -7.7% in placebo group, $p<0.14$).

No significant effect could be seen with regard to other outcome measures, including oral opening, grip strength, flexion index, functional index, HAQ or patient global assessment.

Thirteen (37%) patients withdrew from the MTX group and 11 (31%) patients from the placebo group, mainly due to treatment inefficacy. Only 1 patient dropped out because of adverse event (oral ulcers on MTX treatment).

In summary, the results of the two randomised controlled trials (RCTs) indicate that MTX improves skin changes in early dSSc. However, its clinical effect is of borderline value. No significant improvement in internal organ manifestations could be demonstrated with MTX therapy. The withdrawal rate was high in both trials, mainly due to treatment inefficacy or SSc-related complications. Toxicity of MTX was low, and included mainly transient abnormalities in liver enzymes or oral ulcers, which are well-known side effects of MTX therapy.

It should be noticed that these studies

have several limitations. The number of patients included in the RTCs was rather low and therefore could be underpowered to detect smaller effects, in particular for internal organ involvement. Of interest, recent re-analysis of the data from the multicenter study using Bayesian analysis suggests that MTX has a high probability of beneficial effects in SSc for skin disease and global assessment (9). The probability that treatment with MTX results in better mean outcomes than placebo was 94% for mRSS, 96% for UCLA skin score and 88% for physician global assessment. Moreover, the doses of MTX used in both trials were also lower than that used in current clinical practice. This fact might be responsible for low efficacy but also low toxicity of MTX observed in these RCTs.

Notably, the mild positive effects of MTX on skin fibrosis in early dSSc are not unique for MTX, but have been demonstrated also with other immunosuppressive regimens including oral cyclophosphamide (10). Some other immunosuppressive treatments, such as mycophenolate mofetil or cyclosporine, which have not yet been investigated in the setting of RCTs, have also shown potentially beneficial effects on skin changes in open-label or retrospective studies (11, 12). Overall, it appears that the mild effects on skin fibrosis of borderline clinical value might be shared between different immunosuppressives.

However, as long as convincing alternatives for the treatment of fibrotic manifestations are not available, it seems at present reasonable to consider MTX as a treatment option in SSc patients with progressive diffuse SSc and in whom the efficacy/risk ratio favours MTX over other immunosuppressive drugs or who cannot tolerate other immunosuppressive treatments. Accordingly, MTX has been recommended for treating skin changes in patients with early diffuse SSc (13).

Despite the lack of specific randomised clinical trials, MTX, due to its anti-inflammatory actions and relatively good safety profile, is also considered the treatment of choice in patients with SSc/inflammatory arthritis and SSc/

myositis overlap syndromes in whom musculoskeletal manifestations dominate in the clinical picture (14). Indeed, MTX is frequently used in clinical practice despite its limited evidence for efficacy (15). SSc patients who might particularly benefit from treatment with MTX are patients suffering from polyarthritis or polymyositis, either as part of the SSc disease spectrum, or as part of an overlap syndrome. In these patients, MTX therapy might allow sparing higher doses of steroids which have been associated with risk of scleroderma renal crisis in retrospective analyses, a life threatening complication of SSc (16).

There are controversies regarding the potential role of MTX in inducing interstitial lung disease in SSc. MTX might induce lung injury through allergic, cytotoxic or immunologic reactions (17, 18). This effect is infrequent, unpredictable and usually develops in close relationship with the start of MTX therapy. The limited data available from the two RCTs in SSc did not however show worsening of lung function in MTX-treated patients for up to 12 months (7, 8). Taking into account the risk of development of disease-related lung fibrosis and possible MTX-related pulmonary complications, regular monitoring including past medical history, physical examination and pulmonary function tests, is advisable to identify early potential pulmonary complications.

Mechanisms of action of MTX in fibrotic conditions

The mechanisms of action of MTX in SSc are not fully clarified. MTX, as an anti-inflammatory and immunosuppressive agent, might act through decreasing systemic immune and inflammatory reactions as well as through diminishing local inflammatory infiltrates which are found in the skin and internal organs in the early stages of SSc. However, the inflammatory infiltrates are usually sparse even in the early stages and are limited in the skin to perivascular locations. In contrast, profibrotic cytokines are expressed by resident cells such as fibroblasts and endothelial cells throughout different

disease stages (19). MTX might therefore mediate its effect through suppression of profibrotic factors, although this has not been analysed in great detail (20). It remains unclear whether MTX might directly inhibit extracellular matrix synthesis, which is considered the key pathology in SSc. The limited evidence from experimental studies does not support direct anti-fibrotic effects of MTX. A recent report did not show beneficial effects of MTX in bleomycin-induced skin fibrosis in mice (21). On the other hand, some experimental studies suggest that MTX might even stimulate fibroblast function. In the study by Van den Hoogen *et al.*, MTX stimulated in a dose-dependent manner *in vitro* synthesis of glycosaminoglycans by normal and SSc fibroblasts (22). Moreover, adenosine, a key molecule in the anti-inflammatory action of MTX seems to have a pro-fibrotic effect in some experimental models, thereby suggesting a mechanism through which MTX could lead to a fibrotic process (23). Since the pathogenesis of SSc is complex, further studies are required to clarify impact of MTX on development of fibrosis in SSc.

Use of methotrexate in mixed connective tissue disease

Mixed connective tissue disease (MCTD) is an autoimmune systemic disease characterised by the presence of high titers of anti-U1-RNP autoantibodies. Typical clinical features include puffy fingers, acrosclerosis, Raynaud's phenomenon, myositis and synovitis. Features common to other connective tissue diseases might also develop, including pulmonary arterial hypertension, while severe kidney and CNS-involvement are rare in MCTD. MCTD has been considered a "go-through state" by some authors, because as much as 50% of patients with MCTD fulfil the classification criteria for other connective tissue diseases during follow-up, mostly SSc, SLE and RA. However, several genetic, serologic and clinical features support the concept of MCTD as its own disease entity (2).

No controlled clinical trials have been published to guide therapy in MCTD, and therefore treatment strategies

largely rely upon conventional therapies that are used for similar problems in other rheumatic conditions. MTX is therefore most often used in MCTD when polyarthritis or myositis is prominent and cannot be controlled by other treatments. Indeed, musculoskeletal symptoms are frequent in MCTD and include non-specific arthralgias and myalgias, arthritis and myositis. The joint involvement in MCTD tends to be more severe than in SLE and SSc. Inflammatory arthritis is often the presenting symptom of MCTD and occurs in 60–100% of patients with MCTD. The arthritis in MCTD can be erosive in 30–70% of patients by x-ray. However, the course of MCTD associated inflammatory joint disease is usually more benign than that of erosive RA. Arthritis mutilans can also occur in rare cases. The prevalence of myositis in MCTD varies from 15–75% in different studies. Myositis is often present early in the course of the disease and manifests as acute flares. Less often, myositis presents as a low grade and persistent manifestation (2). While MTX is often used in clinical practice for these patients, published evidence concerning the efficacy and safety of MTX in MCTD is limited and consist mainly of single case reports and expert opinions (24, 25).

Conclusions

Despite lack of evidence from disease-specific RCTs, MTX is used in clinical practice to treat SSc- and MCTD-related musculoskeletal manifestations not responding to other therapies such as non-steroidal anti-inflammatory drugs. The results from two RCTs indicate that MTX modestly improves skin changes in early dSSc. However, its clinical effect is of borderline significance. At present, available evidence does not support usage of MTX for treating internal organ involvement in SSc. However, clinical trials evaluating efficacy of MTX in SSc might have been per-

formed with lower than optimal MTX dosage, making definite conclusions on the efficacy of MTX in SSc difficult. Regular follow-up of patients treated with MTX for SSc or MCTD is of key importance for monitoring treatment efficacy and safety in individual patients.

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