
Use of methotrexate in patients with systemic lupus erythematosus and primary Sjögren's syndrome

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ABSTRACT

While there is still no convincing evidence that methotrexate is of benefit in primary Sjögren's syndrome, the SLE evidence on this rheumatology anchor drug is substantial. In fact, there are randomised controlled trials showing the benefit for methotrexate on overall SLE activity, reduction in glucocorticoid doses, and effects on lupus arthritis and lupus skin manifestations. In addition, methotrexate may be helpful in vasculitis, haematological manifestations, and perhaps kidney disease. Intrathecal methotrexate was successfully used in neuropsychiatric SLE. Taken together, using methotrexate in SLE is not only a common approach, but, at least in part, supported by evidence from clinical trials.

SLE is characterised by a wide variety of autoantibodies and immune complexes, some of which are definitely pathogenic. These autoantibodies are produced by plasma cells and B cells that have received help by T cells, which in turn have found the antigen presented by dendritic cells or B cells (1). Immune complex deposition leads to Fc receptor and complement dependent, presumably macrophage driven, inflammatory processes that result in the organ inflammation ultimately causing the disease (2). Many of these processes could therefore be targets for the therapeutic action of methotrexate. However, data on methotrexate in the disease are quite limited. Regarding the prevalence of 60–100 per 100,000 women, SLE is not exactly a rare disease. However, because of its variable presentation and pattern of organ manifestation and its undulating course, it has not been an inviting background for clinical trials. Nevertheless, the EULAR recommendations for the management of systemic lupus erythematosus include methotrexate therapy in

SLE (3). This analysis resulted in a recommendation with a relatively high category of evidence (2), with an 80% level of agreement among the experts. Only two controlled trials have been published, namely by Carneiro and Sato (4), and by Fortin *et al.* (5), including a total of 41 and 86 patients, respectively. Carneiro and Sato used 15–20mg/week. Fortin *et al.* started with a very low dose of 7.5mg/week titrated in 2.5mg steps up to 20mg/week. Both these trials found a significant decrease in glucocorticoids in the methotrexate arm, and a decrease in disease activity. Carneiro *et al.* randomised 20 patients with mild (to moderate) SLE to 20mg methotrexate q. week (15mg if below 50kg) and 21 to placebo (4). The mean SLEDAI was 8.7 and 9.4, the mean prednisone dose 17.5 and 16.4mg for the methotrexate and control group, respectively. Two placebo patients discontinued the study due to severe flares, and two methotrexate patients left the study because of side effects. Thirty-seven patients completed the study. The mean SLEDAI scores were significantly better in the methotrexate arm from month 3, and mean prednisone doses were significantly lower from month 4 on. Thirteen patients in the methotrexate arm, but only one patient in the control arm, reduced their prednisone by at least 50%. Mean prednisone was reduced from 18mg q.d. to 10mg q.d. in the methotrexate arm and had to be increased from 16mg q.d. to 24mg q.d. in the placebo arm. Organ-specific effects are reported below.

Fortin *et al.* randomised 41 patients to methotrexate 41 and 45 to placebo (5). The mean SLEDAI was 10.0 both in the methotrexate and the placebo arm, the mean steroid dose 7.1 vs. 4.9mg/day, 46% and 51% were not on steroids. Sixty patients completed the study. In the methotrexate arm, 5 patients discontinued because of adverse events,

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7 because of flares/SLE activity, while the respective numbers were 0 and 10 in the placebo arm. Two patients of each arm were lost to follow up. Decrease in steroid dose significantly favoured the methotrexate arm (-22%, $p=0.01$). In the methotrexate arm, 10 patients (24%) were able to reduce their prednisone while 2 patients (5%) to discontinue prednisone. In the placebo arm, 1 patient discontinued prednisone (2%), while 6 (13%) decreased their prednisone. The SLAM-R was significantly lower in the methotrexate group (mean during-trial difference -0.856 $p=0.039$).

Most of the other evidence stems from relatively small uncontrolled series, as reviewed by Sato (6) and by Wong and Esdaile (7). These series suggest differential effects by organ manifestation. Therefore, in this review, we will try to present the evidence for each major organ manifestation.

Musculoskeletal involvement

Joint involvement is the most frequent non-organ-threatening disease manifestation of SLE. Arthralgias are reported with a frequency of 80% to 100% during the course of SLE, consistent with 81% of SLE patients reporting joint pain as an important problem in their disease (8). Arthritis is less common, but still with a frequency of up to more than 50% (9).

In other arthritides, prominently including rheumatoid arthritis and psoriatic arthritis, there is ample evidence that methotrexate is useful (10-12). By analogy, methotrexate is not uncommonly used in patients with lupus arthritis. For most early reports, the weekly dose of methotrexate was clearly suboptimal from today's perspective. Among those in the higher dose range, Wise *et al.* found that 6 out of 13 patients with arthritis responded (13). Gansauge *et al.* reported that 15mg of methotrexate per week led to remission in 10 of 12 patients with lupus arthritis (14). In a retrospective cohort-study including patients with antimalarial-resistant arthritis, 15/17 patients receiving methotrexate experienced an improvement of at least 60% in the joint count at six months, in contrast to only 2 of 17 pa-

tients in a matched control group (15). In fact, mean joint counts decreased from 17.6 to 5.0 in the methotrexate group, while increasing from 6.6 to 8.3 in the control group. Four out of 17 patients in the methotrexate group and 2 out of 17 in the control group went into arthritis remission. Analysis of our own experience gave results in the range of these reports (16). Out of 193 SLE patients, 50 had at least one episode of arthritis. Methotrexate was used in 31 arthritis episodes, and continued with success in about two thirds (20/31).

The two controlled trials both included patients with arthritis. Unfortunately, Fortin *et al.* do not give detailed data on the more than 90% of patients with musculoskeletal involvement (5), but such a considerable proportion of patients would preclude a positive outcome if there were no effect. In the Carneiro trial, 16 out of 17 patients in the methotrexate group experienced remission of their arthritis, *versus* only 1 of 17 in the control group ($p<0.001$) (4). From one month on, articular pain VAS values were significantly better in the methotrexate group.

The evidence is much less convincing and limited to case reports in the use of methotrexate in myositis (13). In the above-mentioned series by Wise *et al.*, the only patient with myositis responded. In 1988, Rothenberg still reported myositis remission in one of two patients with a low dose of 7.5mg/week (17).

SLE skin disease

Skin manifestations are likewise very common in SLE, while other patients have cutaneous lupus only, without fulfilling criteria for SLE. Nevertheless, it is probably safe to include cutaneous lupus when analysing the effect on skin manifestations. In a case report on a patient with subacute cutaneous lupus (SCLE) who was successfully treated with 25mg of intravenous methotrexate q.week, Kuhn *et al.* reviewed several other case reports, which in total suggested effects on both SCLE and discoid lupus (DLE) (18). Gansauge *et al.* reported disappearance of symptoms in 8 of 10 patients with a refractory SLE rash (14). Wenzel *et al.* reported

on 43 patients, of whom only 7 had SLE, in the largest retrospective series published (19, 20). These patients were treated with an intravenous dose of 15-25mg methotrexate q. week; the dose was reduced to 7.5-15mg i.v. in 8 patients and switched to 10.20mg p.o. in another 7. In a second report, the authors demonstrated that switching to s.c. methotrexate in 15 of their patients maintained the therapeutic effect (20). In the 43-patient study, using the "cutaneous lupus activation index (CLAI)", 42 of the 43 patients experienced improvement, with the mean CLAI falling from 5.3 at baseline to 1.6. In particular, the 16 patients with SCLE and the 8 patients with localised DLE responded very well. In addition, among 10 patients with initial lymphocytopenia, lymphocyte cell counts increased significantly. Refractory mucosal lesions, which are also part of the clinical spectrum of SLE, may likewise respond to methotrexate (21), as may skin vasculitis (14) and bullous lesions (22). Like with musculoskeletal symptoms, both controlled trials include SLE patients with skin manifestations, either DLE or malar rash, which resolved in 9 of 12 patients in the Carneiro study, as compared to 0 of 16 in the control arm ($p<0.001$) (4).

Vasculitis

Both large and small vessel vasculitides have been shown to respond to methotrexate (23-25). Again, by analogy, mild to moderate lupus vasculitis is one possible reason for instituting methotrexate. Remission was achieved in 6 out of 9 patients with vasculitic lesions under 15mg of weekly oral methotrexate in the series by Gansauge (14). A similar effect was observed in one patient with skin and possibly gastrointestinal vasculitis in the series by Rothenberg *et al.* (4).

CNS lupus

Although neuropsychiatric lupus (NPSLE) disease is now known to be uncommonly caused by vasculitis (26), methotrexate therapy has been tried in several centres. While the effects of oral and parenteral methotrexate appeared quite variable in neuropsychiatric SLE

Table I. Overview of evidence on methotrexate efficacy in SLE.

| | Effect | Evidence | References | Notes |
|-------------------|--------------|----------|------------|-----------------------|
| Disease activity | convincing | Ib | (3-5) | |
| Arthritis | convincing | Ib* | (8, 13-15) | |
| Myositis | probable | IV | (13, 17) | |
| Malar rash | probable | Ib* | (14) | |
| SCLE | convincing | Ib | (18) | |
| DLE | convincing | Ib* | (18) | |
| Bullous lesions | possible | IV | (22) | |
| Mucosal lesions | possible | IV | (21) | |
| Vasculitis | probable | Ib | (4, 14) | |
| NPSLE | probable | III | (27-29) | intrathecal |
| Nephritis | questionable | III | (5-7) | CAVEAT renal function |
| Serositis | questionable | III | (7, 13) | |
| Lymphocytopenia | probable | III | (20) | |
| Haemolytic anemia | possible | Ib | (35) | paediatric |
| Thrombocytopenia | possible | III | (34) | |

*not as a predefined outcome

(17, 27), intrathecal methotrexate with intrathecal dexamethasone was associated with a response in two series. Valesini *et al.* reported on three patients suffering from acute transverse myelitis, hemiparesis and signs of focal and diffuse cerebral dysfunction, respectively, being treated intrathecally with 10mg of methotrexate and 20mg of dexamethasone (20mg). Each experienced a significant improvement of neurologic symptoms (28). A larger study included 24 patients refractory to conventional steroid therapy. Symptoms were reported to be significantly reduced in 22 out of these 24 patients after the intrathecal application of methotrexate (10–20mg) and dexamethasone (10–20mg) (29).

Lupus nephritis

In contrast to the manifestations above, one might think that methotrexate is a dangerous choice based on the fact that methotrexate is toxic with even moderately decreased renal function (30). Nevertheless, several case series have assessed MTX in lupus nephritis (6, 7) despite early negative results (31). For example, Walz, LeBlanc and colleagues have reported success in all three patients with lupus nephritis (32). Unfortunately, Fortin *et al.* have not reported on renal outcome in the more than 40% of patients with renal involvement in their controlled trial (5), and more complete reports on successful series of lupus nephritis patients

under methotrexate have so far only been published in abstract form (7).

Serositis

Although serositis is a typical and relatively common manifestation of SLE, there is no convincing evidence that methotrexate has any major effects in adult SLE patients. Among three documented patients with serositis, only one improved in the series by Wise *et al.* (13).

Haematology

Methotrexate may also relieve haematological symptoms of SLE. In their series with cutaneous lupus treated with methotrexate, Wenzel *et al.* reported an increase of lymphocyte counts among 10 patients with initial lymphocytopenia (from 0.72 ± 0.06 to $1.12 \pm 0.07 \times 10^9$ cells) (20). One case report described clinical remission of acquired thrombasthenia, probably due to autoantibodies against GP IIb/IIIa induced by low dose methotrexate (33). In children, effects on thrombocytopenia (34) and haemolytic anaemia (35) have also been reported.

Side effects of methotrexate in SLE

Several studies have suggested that some of the adverse events may occur more commonly than in RA or psoriatic arthritis (4, 5, 15, 20). For example, Wenzel *et al.* reported liver enzyme elevations in 23 out of 34 patients and

moderate pancytopenia in 7. While adverse events led to 5 withdrawals in the Fortin trial and 2 withdrawals in the Carneiro trial, no adverse event-related withdrawals in each of the respective were reported. Neither of the controlled studies found a significant difference in specific events between the two arms, and no unusual adverse events were reported.

Methotrexate and Sjögren's syndrome

The evidence is practically absent for primary Sjögren's syndrome. There is one open label study of 0.2mg/kg body weight q. week with 17 patients suggesting improvement only in subjective parameters. Seven patients had persistent elevations of liver enzymes (36).

Conclusions

In summary, there are no trials supporting efficacy of methotrexate in Sjögren's syndrome; unfortunately, arthritis in Sjögren's has simply not been studied. In contrast, while still limited, there is class Ib evidence that methotrexate in the RA range works for SLE, with effects on arthritis and skin disease. Controlled trials have shown an overall benefit on disease activity associated with reduced corticosteroid use, and suggest an acceptable safety profile. In addition, case reports and small series suggest that methotrexate may work for other mucocutaneous and musculoskeletal manifestations, as well as for lupus vasculitis and some haematological manifestations. Intrathecal methotrexate may constitute an option for NPSLE, and the books on methotrexate in lupus nephritis are not yet closed. Larger randomised controlled trials would be helpful to better position methotrexate in lupus therapy.

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