Use of methotrexate in patients with psoriasis

A. Kuhn, V. Ruland, N. Patsinakidis, T.A. Luger

Department of Dermatology, University of Münster, Münster, Germany.

Annegret Kuhn, MD, Professor
Vincent Ruland
Nikolaos Patsinakidis, MD
Thomas A. Luger, MD, Professor

Please address correspondence to:
Prof. Annegret Kuhn, MD,
Department of Dermatology,
University of Münster,
Von-Esmarch-Straße 58,
D-48149 Münster, Germany.
E-mail: kuhnan@uni-muenster.de

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ABSTRACT

Psoriasis is considered to be a polygenetically influenced, immune-mediated, organ-specific disease of dysregulated inflammation that is triggered by environmental factors such as infections, medications, and physical and/or emotional stress. It is recognised as one of the most prevalent skin diseases, affecting 2% to 3% of Caucasian populations. Major advances in understanding of disease pathogenesis indicate that patients with psoriasis have an increased risk of comorbidities such as metabolic syndrome and cardiovascular disease. A wide range of systemic drugs have been developed in recent years for treatment of psoriasis and comorbidities. Low-dose methotrexate (MTX) is one of the classical agents and is still one of the most frequently used systemic treatments for psoriasis worldwide. Low-dose MTX is also effective in treatment of psoriatic arthritis. The mechanism of action is not fully understood, but MTX is suggested to act primarily as an anti-inflammatory and immunosuppressant drug. A favourable efficacy and safety profile has been established for MTX in a large number of clinical trials, as well as in common practice. This review summarises the nature of the disease and our present knowledge about MTX in the treatment of psoriasis, including combination therapies.

Psoriasis

Psoriasis is one of the most common chronic, immune-mediated inflammatory diseases involving the skin, nails, and joints. With its early onset and its chronic relapsing nature, psoriasis may significantly impair a patient's physical health, mental functioning, and well-being. The condition affects about 2% to 3% of the Caucasian population worldwide; it may begin at any age, but has peak incidence in the second and third decades of life (1).

Patients with psoriasis face extensive personal expense, as well as possible strong stigmatisation and social exclusion; therefore, the management of psoriasis should include medical treatment, patient counselling, and psychosocial support, if needed. Moreover, there is a significantly increased risk of comorbidities, such as diabetes mellitus, metabolic syndrome, and cardiovascular disease, likely linked to the underlying chronic inflammatory nature of the disease (2, 3).

Psoriatic arthritis (PsA), a seronegative, chronic inflammatory arthropathy, is seen in about 10% to 30% of patients with psoriasis, although wide variation in prevalence has been reported (4, 5). Clinical manifestations of psoriasis that are associated with a higher incidence of PsA include nail dystrophy, lesions of the scalp, and intergluteal/perianal lesions (4) (*see page S132 for Psoriatic Arthritis*). Moreover, psoriasis patients are at greater risk than the general population for development of lymphomas or skin cancer, although it remains unclear whether this risk is associated with psoriasis, its treatment, or both (6).

Various quantitative measures are used to assess the severity of psoriasis. These include a "physician global assessment" (PGA), estimation of the affected "body surface area" (BSA), and the now commonly used "psoriasis activity and severity index" (PASI). This index is calculated from the clinical findings of erythema, infiltration, and scaling as well as the affected body surface area. PASI 75 for example specifies the percentage of patients who achieved a 75% improvement of the PASI. More recently, questionnaires about the disease-specific quality of life (DLQI) have been developed and used in clinical trials. Currently patients with a BSA>10, a PASI>10, and a DLQI>10 are considered as having moderate to severe disease (7).

The most common type of disease is psoriasis vulgaris, which is associated with a wide range of skin manifestations, including plaque psoriasis, gut-

tate psoriasis, and pustular psoriasis, among others. Plaque psoriasis is characterised by focal formation of inflammatory (erythematous and oedematous) plaques that are covered by white or silvery scales resulting from an excessive growth of skin epithelial cells. The psoriatic plaques are well-delineated from surrounding normal skin and are usually distributed symmetrically, typically seen at the extensor surfaces of the extremities, scalp, lumbosacral region, and umbilicus (8). Approximately 10% of patients with psoriasis suffer from the Koebner phenomenon, also known as the isomorphic response, which refers to induction of new psoriasis lesions in uninvolved skin following local trauma or injury to the skin (9).

Distinctive disease-related nail changes occur in approximately 50% of patients with psoriasis. The most common sign is pitting (presence of small depressions on the nail surface); also onycholysis (separation of the nail plate), oil spots (orange-yellow subungual discoloration), and nail dystrophy are seen as characteristic features of the disease (Fig. 1).

In general, the common characteristic of psoriasis is the coexistence of cutaneous inflammation, histologically seen as a compact leukocytic infiltration with dilated, prominent capillaries in the upper dermis and epidermal hyperproliferation, resembling a massive acanthosis, accompanied by hyper-, parakeratosis, and papillomatosis. In recent years, considerable progress has changed our understanding of the pathophysiology and pathogenesis of psoriasis. Most of the knowledge in this area is derived from clinical trials and translational science performed in patients with the disease, due to the lack of a generally accepted animal model (10).

Psoriasis is currently regarded as a complex, genetically programmed disease with environmental components (stimuli) (11). Increasing evidence indicates that the pathogenetic progress of the psoriatic inflammation is driven from an immune-mediated process comprised of cells and mechanisms of the non-specific and specific immune system (known as innate and adaptive immunity, respectively). Psoriasis is characterised by the presence of several dendritic antigen-presenting cells. Accordingly, IL-23-producing myelodendritic cells are strongly involved in T-cell activation. Moreover, tumour necrosis factor-alpha (TNF-α)/inducible nitric oxide synthase (iNOS)-producing dendritic cells release several proinflammatory molecules, thus activating keratinocytes and other cells to produce a variety of proinflammatory cytokines, chemokines, and vascular endothelial growth factor (VEGF). These mediators initiate generation and activation of specific subsets of T-cells such as Th-1, Th-17, and Th-22 cells, which are characterised by the production of cytokines, such as interferon-gamma (IFN-γ), IL-17, and IL-22, respectively (11). In addition to modifying skin inflammation, some of these mediators of inflammation may be released into the circulation and cause systemic disease such as metabolic syndrome and cardiovascular disease, particularly in severe cases.

Genetic analysis of affected individuals and families has identified some polymorphisms associated with psoriasis and psoriatic arthritis. The human leukocyte antigen (HLA) Class I allele most highly associated with psoriasis is *HLA-Cw6* (termed *HLA-Cw*0602* when identified by DNA typing), found in 40–80% of individuals with psoriasis in different series, but with a penetrance of only ~10% (12). Therefore, this allele is likely useful as a clue to pathogenesis, but not clinically helpful at this time. Moreover, it has been suggested that low penetrance of *HLA-Cw6* implicates environmental triggers or other co-factors in the pathogenesis of psoriasis. A recently reported genome-wide association scan indicates a strong association of psoriasis with non-HLA genes involved in IL-23 signalling and the NFκB pathway (13).

Until the last decades of the 20th century, psoriasis was regarded by many patients and physicians as a disease purely confined to the skin and was simply treated with various topical agents (*i.e.* corticosteroids, vitamin D-3 derivatives, and anthralin), ultraviolet light (UV), or both. Although most patients with mild to moderate psoriasis benefited from these therapeutic strategies, efficacy was limited in more severe cases because of the risk of adverse cutaneous effects associated with long-term treatment. Over the past fifty years, however, various systemic agents have been evaluated and approved for the treatment of moderate to severe psoriasis. Almost all have different mechanisms of action, interfering at various stages of the pathogenesis of the disease. These agents include methotrexate (MTX), cyclosporine, retinoids (such as etretinate and its major metabolite acitretin), and fumaric acid esters (licensed only in Germany) (14).

With recognition of psoriasis as a chronic immune-mediated inflammatory disease of the skin and progress in the field of genetic engineering, more specific therapies – such as monoclonal antibodies that target molecules of the disease pathway – have been developed for psoriasis. These biological agents also provide insights concerning the role of their target antigens in psoriasis. For example, the major pathogenic contribution of T-lymphocytes was best illustrated by the efficacy of drugs such as alefacept and efalizumab (10). Proinflammatory TNF-α plays a central role in the inflammatory process underlying psoriasis. Accordingly, selective agents targeting TNF-α have proven highly effective in treating psoriasis (15).

Approximately one fifth of patients with moderate to severe psoriasis receive TNF-α blockers at this time. The success of anti-TNF therapy has enhanced capacity to dissect the role of this specific cytokine in the multifactorial disease progress. Recently, IL-12 and IL-23, cytokines that induce naive $CD4^+$ lymphocytes to differentiate into Th1 cells and Th17 cells, respectively, have been identified as key mediators of psoriasis (16). A fully humanised antibody that targets the p40 subunit shared by both IL-12 and IL-23, ustekinumab, has shown great efficacy in treating moderate to severe psoriasis. Novel compounds currently being investigated for efficacy in the treatment of psoriasis include antibodies against IL-17, IL-18, VEGF-antagonists, a protein kinase C inhibitor, pan-

selectin antagonists, and JAK/STAT pathway inhibitors, as well as several small modular immuno-pharmaceutical drugs (SMIP) (17). Furthermore, it has been suggested that selective tyrosine kinase inhibitors, commonly used in the treatment of neoplastic diseases, could be possible therapeutic options for the treatment of psoriasis and rheumatic diseases (18).

The complexity of psoriasis and the variable efficacy of multiple drugs render evaluation of treatment options difficult. Considerations before choosing the appropriate treatment for an individual patient include: long-term efficacy and adverse events, the presence of psoriatic arthritis and of specific comorbidities (*e.g.* hepatitis, tuberculosis), and possible need for treatment interruption (*e.g.* by surgery). Central guidelines such as the European S3-guidelines on the systemic treatment of psoriasis vulgaris (7, 19) contribute to clinical decisions. Moreover, registries are helpful in monitoring disease progression over time.

History of MTX treatment in psoriasis

The use of folic acid antagonists in psoriasis originated from a finding by Gubner in 1951 (20), who reported rapid clearing of psoriatic skin lesions in patients treated with aminopterin for rheumatoid arthritis. In the ensuing years, the more stable and less toxic derivative MTX was introduced for the treatment of psoriasis (*see pages S21-S45 for Pharmacology of MTX*). MTX has been used as a therapeutic agent for psoriasis since 1958 (21); the first guidelines concerning MTX therapy for psoriasis were established in 1972 by Roenigk and colleagues (22), with several refinements thereafter (23-25).

About the same time the initial guidelines were written, the United States Food and Drug Administration (FDA) approved MTX for use in severe, recalcitrant disabling psoriasis after evaluation of its side-effect profile. Interestingly, FDA approval was not based on the results of double-blind, placebo-controlled trials, which currently are a prerequisite for any new drug approval in the US. In the 1970s and 1980s, some small studies investigating MTX in psoriasis were published (26-29); however, only few comply with the current methodological criteria applied to clinical trials. In addition, the PASI was not developed until 1978 (30), rendering objective comparison of outcomes difficult. In recent years, the efficacy of systemic agents for psoriasis was evaluated by the percentage of patients achieving a 75% reduction of the baseline clinical severity as assessed by the PASI (PASI 75). Nevertheless, clinical experience with MTX is far greater than the documentation of its efficacy in clinical trials (19).

Clinical trials and observational studies of MTX in psoriasis

Monotherapy

For the treatment of psoriasis, MTX is usually given 1x/week either orally, parenterally, or subcutaneously. An initial dose of 5–15mg/week is recommended and may be increased up to 22.5mg/week for maintenance. Because of its onset of action over 4–8 weeks, MTX is not suitable for short-term induction therapy. After 16 weeks, a PASI 75 can be expected in about 60% of patients. Major contraindications include pregnancy, liver dysfunction, liver fibrosis or cirrhosis, pneumonia, alveolitis, bone marrow depression, and renal damage (*see page S95 for Side Effects of MTX*) (7).

Several retrospective analyses have evaluated the efficacy of MTX in patients with psoriasis. In 2000, Haustein and colleagues published a 26-year retrospective study including 157 patients who had been treated with low-dose MTX (15–20mg maximum weekly dosage), with a mean cumulative dose of 3,394 mg and a mean duration of treatment of 237 weeks (4.5 years). The efficacy of MTX was found to be good in 76% of patients, moderate in 18%, and poor in 6%, while 61% patients experienced side effects and 20% were forced to discontinue treatment. Side-effects included abnormal liver function, gastrointestinal discomfort, hematopoietic suppression, and hair loss, among others (31). A similar retrospective analysis by a group from the Netherlands demonstrated prolonged clearing in 81% of 113 psoriasis patients treated with a weekly maximum dosage of 15mg MTX (32). It should be noted that neither study fulfilled the methodological quality inclusion criteria of the European S3-guidelines for the systemic treatment of psoriasis, listed in Appendix I in the corresponding publication (19).

Three studies of MTX monotherapy in psoriasis fulfilled the European S3-guidelines inclusion criteria (Table I). Two small studies from the early 1970s demonstrated a high efficacy of MTX in psoriasis: Nyfors and colleagues showed clearing of the skin lesions in 62% of 50 patients (27) and Weinstein and colleagues reported an improvement of at least 75% of skin lesions in 77% of 25 patients (29). According to the authors of the European S3-guidelines, both trials failed to provide detailed information on the time at which success was assessed, and the PASI was not available for either study. The third study (33) is a more recent randomised controlled trial including 88 patients with moderate to severe psoriasis who were randomly assigned to either MTX (44 patients, 15–22.5mg per week) or cyclosporine (44 patients, 3–5mg/kg bodyweight). The primary end point of PASI 75 response after 12 weeks was achieved by 60% of patients treated with MTX and 71% of patients treated with cyclosporine. However, 40% of patients treated with MTX achieved PASI 90 *versus* 33% of patients treated with cyclosporine, but differences between the two groups were not statistically significant.

Flytstrom and colleagues compared MTX to cyclosporine in a randomised controlled study with 68 patients (34). The 37 patients in the MTX group received a maximum of 15 mg per week, and 5 mg folic acid was administered daily except on days when MTX was given. This group showed a mean PASI change of 58% from the baseline after 12 weeks, compared to 72% in the cyclosporine group. In the CHAMPION study (Comparative Study of Humira *vs*. Methotrexate *vs*. Placebo in Psoriasis Patients) by Saurat and colleagues, MTX was compared to adalimumab and placebo in a randomised, double-blind,

Table I. Clinical trials of methotrexate in psoriasis.*

Author	Year	Design	Intervention	No. of Patients	Follow-up	Outcome
Monotherapy						
Flytstrom *et al*. (34)	2008	MTX *vs*. cyclosporine, randomised controlled trial	7.5 mg MTX per week, increased to 15 mg per week	37	12 weeks	Cyclosporine more effective in PASI change
Saurat *et al*. (35)	2008	MTX *vs*. adalimumab vs. placebo, randomised controlled trial	7.5 mg MTX per week increased to 25 mg per week	110	16 weeks	Adalimumab significantly superior to MTX
Heydendael *et al*. (33)	2003	MTX *vs*. cyclosporine, randomised controlled trial	15 mg MTX per week for 4 weeks, then 22.5 mg per week	43	52 Weeks	No significant differences
Weinstein *et al*. (29)	1971	MTX cohort study	Maximum dose of 22.5 mg MTX per week	26	n/a	Improvement of at least 75% of skin lesions in 70% of patients
Nyfors *et al*. (27)	1970	MTX cohort study	25 mg MTX per week, then tapered 5 mg at a time	50	n/a	Clearing in 62% of patients, 50% reduction in 20%
Combination Therapy						
Asawanonda *et al*. (40)	2006	MTX in addition to UVB *vs*. placebo UVB, randomised placebo-controlled study	15 mg MTX per week plus standard UVB phototherapy after 3 weeks	24	24 weeks	PASI 90 reduction in 91% of patients in the MTX group, 38% in placebo group
Paul *et al*. (28)	1982	MTX in addition to UVB, cohort study (one psoriasis plaque shielded as control)	3 x 5 mg MTX per week plus standard UVB phototherapy after 3 weeks	26	16 weeks	Clearance of disease in all patients
Morison *et al*. (26)	1982	MTX in addition to PUVA, cohort study	3 x 5 mg MTX per week plus PUVA	30	n/a	Clearance of disease in 28 patients

*Listed studies either fulfil the methodological criteria for inclusion in the European S3-Guidelines (19), or were included in the 2009 National Psoriasis Foundation Consensus Conference (47). MTX: methotrexate; PASI: Psoriasis Area and Severity Index; PUVA: psoralen plus ultraviolet A; UVB: ultraviolet B.

placebo-controlled study (35). The 108 patients in the adalimumab group received an initial dose of 80mg subcutaneously at week 0 and then 40mg every other week. The 110 patients in the MTX group received 7.5mg MTX per week initially, which was increased to 25mg as tolerated. After 16 weeks, the primary endpoint of the PASI 75 was achieved by 36% in the MTX group, 80% in the adalimumab group, and 19% in the placebo group. However, the MTX response was still increasing after 16 weeks, and the maximum effect may not have been reached.

A very recent randomised, active-controlled, multicentre study by Reich and colleagues compared the efficacy of infliximab to MTX in psoriasis. After 16 weeks 42% of patients (n=215) treated with MTX had achieved PASI 75 compared to 78% of patients receiving infliximab (n=653) (36). Despite previous work already accomplished, treatment of many cases of severe disabilities associated with nail psoriasis is still challenging. Due to the availability of biological agents for the long-term treatment of psoriasis, it could be shown in several studies that therapy with anti-TNF agents is particularly effective. However, successful results have been reported after long-term therapy with systemic drugs such as cyclosporine, etretinate, and more recently, with MTX (37, 38).

Moreover, Ho and colleagues (39) compared MTX to traditional Chinese medicine (TCM) as well as placebo in 50 patients with psoriasis, in a randomised, placebo-controlled trial. The mean PASI change from baseline after 6 months revealed an improvement of 73.9% in the MTX group compared to 15.1% in the TCM and 32.0% in the placebo group.

Combination therapy

The combination of MTX with other therapeutic agents such as cyclosporine, etanercept, calcipotriol or narrowband UVB therapy may be advantageous to reduce doses of MTX required, thereby lowering the likelihood of potential side effects. Three studies met inclusion criteria of the European S3-guidelines for systemic treatment of psoriasis in 2009, all of which evaluated the combination of MTX with narrowband UVB or PUVA therapy (Table I) (19). Morison and colleagues treated 30 patients with a 3-week course of MTX, followed by a combination of PUVA therapy and MTX over a mean duration of 5.7 weeks (26). Total remission was seen in 28 of the 30 patients, with mean 9.3 (±3.0) exposures to PUVA therapy and a final UVA radiation dose at clearance of 6.2 (±2.5) J/cm^2. Similar effects were shown by Paul and colleagues, with a complete clearing of lesions after 16 weeks in all 26 patients treated with MTX and UVB therapy (28). Asawanonda and colleagues found that a PASI reduction of 90% was achieved in 91% of patients treated for 24 weeks with 15 mg MTX per week and UVB phototherapy, compared to only 38% of patients treated with placebo and UVB phototherapy (40).

Although not included in the European S3-guidelines, further clinical trials have been published evaluating the combination of MTX with other

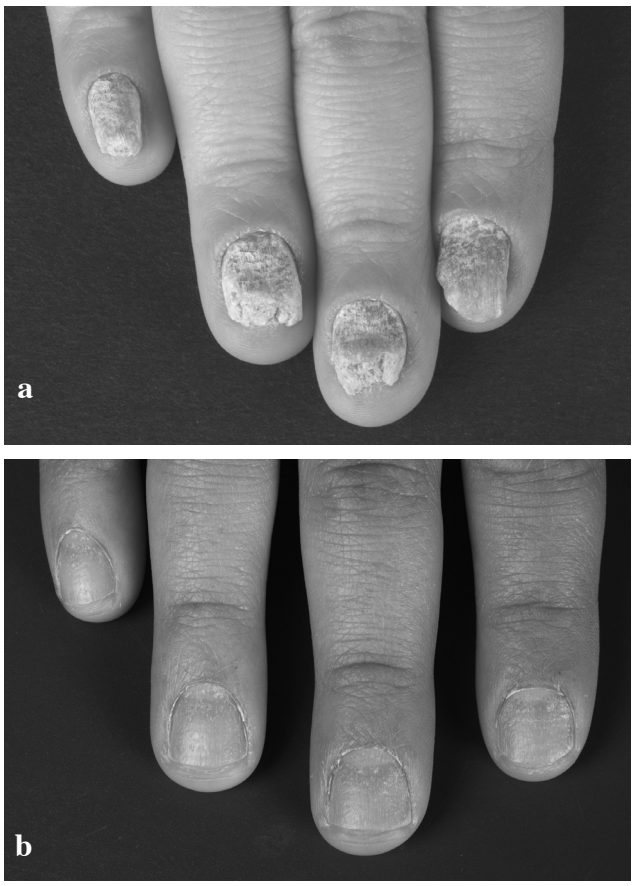

Fig.1. Onychodystrophy of all fingernails in a patient with psoriasis **a**) before and **b**) after 14 months of MTX therapy.

drugs as therapeutic options in patients with psoriasis (Table II). Two clinical trials have been performed to analyse the efficacy of MTX combined with cyclosporine, based on a case report of a psoriasis patient who achieved stable control of his skin and arthritic symptoms with low-dose cyclosporine (mean 2 mg/kg per day) in addition to intramuscular MTX (7.5–20mg per week) for 24 months (41). In a clinical trial conducted by Clark and colleagues, 19 patients with severe recalcitrant psoriasis received a combination therapy of MTX and cyclosporine (42). In combination, the mean dose of MTX was reduced from 21.6±6.7mg per week to 13.9±4.4mg per week, and the mean dose of cyclosporine was reduced from 4.2±1.2mg/kg per day to 2.6±0.9mg/kg per day, while still controlling symptoms. The authors suggested that the combination may also have resulted in reduced use of nonsteroidal anti-inflammatory drugs (NSAIDs) concomitantly in patients with psoriatic arthritis taking cyclosporine, thus reducing possible nephrotoxicity. In a second clinical trial, 20 patients with psoriasis (PASI>12) received the same combination (10mg MTX per week and 3.5mg cyclosporine per kg per day); 14 of these patients (70%) demonstrated good or excellent clinical improvement (43). However, 14 patients also experienced adverse effects, the most common being gastrointestinal symptoms and abnormal renal and/or liver function. It appears that the combination of MTX and cyclosporine induces rapid control of disease activity in acute and severe cases of psoriasis, and doses of either drug can be reduced, which is especially helpful in patients who are resistant to or intolerant of high doses of either drug alone. Nonetheless, further clinical research including observational data with longer follow-up periods is warranted in the future.

The combination of MTX and etanercept has also been evaluated with regard to its efficacy and safety in patients with psoriasis (44). In a pilot study by Zachariae and colleagues, 59 patients were randomly assigned to either etanercept with continuous MTX or etanercept with tapered and discontinued MTX (45). The mean percentage improvement in the PASI 75 scores from baseline at week 24 was 76.4% for the combination group compared to 51.3% for the etanercept/MTX taper group, while no differences were seen in the number of adverse events. The authors concluded that patients with active plaque psoriasis who have inadequate responsese to MTX may achieve additional benefit from the combination with etanercept. These results are similar to those reported by Driessen and colleagues (46) in 14 patients with psoriasis who were treated with MTX and etanercept. Further clinical research is needed to assess the efficacy and safety of etanercept/MTX combination therapy compared to monotherapy with either agent, as combinations of possibly immunosuppressive may lead to a severe immunosuppression and consequently to increased infections and malignancies.

Current guidelines of MTX in psoriasis

In summary, MTX (15 to 22.5mg per week) should be recommended based on the results of the randomised clinical trials and the vast clinical experience with this agent, according to the European S3-guidelines for systemic therapy of psoriasis (19). Clinical experience has shown that the efficacy of MTX, which is the systemic medication for psoriasis with the lowest daily costs, increases with longer treatment. Therefore, MTX should be considered as a primary therapeutic option for long-term therapy. Its clinical application is limited by dose-dependent adverse reactions such as hepatotoxicity, myelosuppression, gastrointestinal ulcers and, very rarely, severe idiosyncratic reactions. However, an acceptable safety profile can be obtained for MTX therapy in most patients with proper selection and monitoring, as well as additional administration of folic acid (19). As discussed, further randomised controlled trials and observational studies concerning combination therapy with new biological agents may lead to safer treatments of patients with psoriasis while retaining the efficacy of a monotherapy.

Table II. Selected clinical trials of methotrexate combined with other therapeutic agents in psoriasis.*

Author	Year	Design	Intervention	No. of Patients	Follow-up	Outcome
Aydin *et al*. (43)	2006	Combination of MTX and cyclosporine, prospective trial	10 mg MTX per week, 3.5 mg/kg cyclosporine per day	20	n/a	Clinically significant improvement in 14 patients
Clark *et al*. (42)	1999	Combination of MTX and cyclosporine, prospective trial	max. 20 mg MTX per week, max. 4.2 mg/kg cyclosporine per day	19	n/a	Good control of both skin and joint problems in all patients
Driessen *et al*. (46)	2008	Combination of etanercept and introduction *vs*. discontinuation of MTX, cohort study	2.5-35 mg MTX per week, 25-50 mg etanercept twice per week	14	96 weeks	Improvement after MTX introduction in 4 of 6 patients and decrease in the PASI improvement after MTX discontinuation in 5 of 8 patients
Zachariae *et al*. (45)	2008	Combination of etanercept and continuous MTX *vs*. MTX tapered and discontinued, randomised controlled trial	7.5-25 mg MTX per week, 25-50 mg etanercept twice per week	59	24 weeks	In 76.4% of combination group and 51.3% of the MTX taper group improvement in the PASI scores
De Jong *et al*. (48)	2003	MTX and calcipotriol *vs*. MTX and vehicle, randomised placebo-controlled trial	2.5-35 mg MTX per week	97	36 weeks	Median time to relapse and dose sparing effects better in the calcipotriol group

*Listed studies are a selection regarding treatment of psoriasis with MTX. MTX: methotrexate; PASI: Psoriasis Area and Severity Index.

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