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# Use of methotrexate in patients with ankylosing spondylitis

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## ABSTRACT

*The disease modifying antirheumatic drug (DMARD) methotrexate (MTX) is widely used and well accepted for the treatment of patients with rheumatoid arthritis (RA). In ankylosing spondylitis (AS), the use of MTX is not recommended for the axial manifestations and may have some efficacy in the peripheral involvement. For this disease there is a lack of clinical trials, and most of the trials did not show efficacy on the axial symptoms of the disease. Furthermore, there is no evidence that MTX increases the effects or prevents the side effects of TNF-blockers if given in combination. In this paper the available data of MTX in AS will be discussed.*

## Introduction

Ankylosing spondylitis (AS) is a frequent inflammatory rheumatic disease with a prevalence of about 0.5% (1, 2). Among the group of spondyloarthritides (SpA), AS is the major subtype of a group of diseases consisting of AS, psoriatic SpA, reactive SpA, SpA associated with inflammatory bowel disease, and undifferentiated SpA (3). The most important clinical manifestations are inflammatory back pain (IBP), asymmetric peripheral oligoarthritis, predominantly of the lower limbs, enthesitis, and specific organ involvement such as anterior uveitis, psoriasis and chronic inflammatory bowel disease (4). The SpAs are genetically linked, and the strongest known contributing factor is the major histocompatibility complex (MHC) class I molecule HLA-B27.

The diagnosis of AS has been made since 1984 according to the modified New York criteria and requires the presence of sacroiliitis of at least grade II bilaterally or grade III unilaterally on plain radiographs and at least one clinical criterion (5). However, the diagnosis of AS is delayed over 5–10 years after the occurrence of the first symptoms, probably owing to the delay of evidence

of sacroiliitis on plain radiographs (6). It has been proposed that patients with predominant axial SpA and AS should be considered as belonging to one disease continuum, called axial SpA, irrespective of the presence or absence of radiographic changes (6), which is also reflected in the new ASsessment in SpondyloArthritis (ASAS) classification criteria for axial SpA (7).

## Methotrexate in ankylosing spondylitis

Until ten years ago, non-steroidal antirheumatic drugs (NSAIDs) and physical therapy were the only established treatment for ankylosing spondylitis. During the last decade the tumour necrosis factor (TNF)- $\alpha$  blocking agents infliximab (8, 9), adalimumab (10), etanercept (11, 12) and golimumab (13) were shown to be highly effective in active ankylosing spondylitis and resistant to NSAID treatment, and were approved for the market. All of them reached about a 50% improvement of disease activity as measured by the patient-based disease activity score "Bath Ankylosing Spondylitis Disease Activity index (BASDAI)", and led to improvements in mobility, function, C-reactive protein and quality of life.

However, there is no evidence that disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine, which have high efficacy in the treatment of rheumatoid arthritis and are regarded as the preferred treatment for active forms of rheumatoid arthritis, have any role in the treatment of the axial manifestations of ankylosing spondylitis.

Sulfasalazine has shown to be effective for the peripheral joint involvement in ankylosing spondylitis and other SpA, but not for axial symptoms (14, 15). This is also reflected in the current ASAS/European League Against Rheumatism recommendations for the management of ankylosing spondylitis (16).

*Conflict of interest: Dr Haibel has received speakers' honoraria from Abbott, MSD Europe and Wyeth; Dr Sieper receives consultancy fees from Abbott, Pfizer, MSD Europe, Roche and UCB.*

Surprisingly, despite the lack of evidence of any efficacy, several reports are detailing treatment with DMARDs of up to 40% of patients with ankylosing spondylitis, preferentially with sulfasalazine and methotrexate (17-20). In most of these manuscripts information about a correlation between DMARD treatment and the presence of concomitant peripheral arthritis was not given. Methotrexate has been tested to date in three randomised controlled trials with a dosage between 7.5 and 10mg/week *versus* placebo, with treatment durations between 12 and 24 weeks. It was not superior to placebo in two of these studies (21, 22). Only in one study with a high percentage of patients with concurrent peripheral arthritis a better response in some of the outcome variables was found (23).

In the Altan 2001 trial (21), only the physician global assessment showed a significant difference between the placebo and MTX group, with the group receiving MTX favoured over the group that received no MTX. No statistically significant differences between the intervention groups in function index, spondylitis index and enthesitis index were found. In the Roychowdhury 2002 trial (22), the changes from baseline of BASDAI, Bath ankylosing spondylitis metrology index (BASMI) and CRP (mg/L) over 24 weeks were assessed. No significant differences were found between the MTX and the placebo group. In the Gonzalez-Lopez 2004 trial (23), the primary outcome was the response rate in a composite index, which was defined by improvement of  $\geq 20\%$  in at least five of the following areas with no worsening in any of the scales ( $>20\%$  worsening compared to baseline): severity of morning stiffness, physical well being; BASDAI; Bath ankylosing spondylitis functional index (BASFI); Health assessment questionnaire for spondyloarthropathies (HAQ-S); physician global assessment; patient global assessment. At week 24 this composite index showed significant difference between the intervention groups, favouring the group on MTX over the placebo group (RR 3.18, 95% CI 1.03 to 9.79 (Comparison 01.01) and NNT=3) For secondary outcomes, including those

seven outcomes for response judgment mentioned above, no statistically significant differences were found between the MTX and the placebo group.

A similar result was obtained in an open study of 34 patients treated with methotrexate given intramuscularly at a dose of 12.5mg/week over one year (24). All the patients presented with active axial disease, including elevated ESR  $\geq 25$ mm and failure of treatment with non-steroidal anti-inflammatory drugs for a period of more than two years. Fifty-three percent were considered responders to MTX; most of them presented with peripheral arthritis. Despite clinical improvement, axial measures were unaltered at the end of the study. The mean value of ESR decreased significantly at the end of the treatment ( $p < 0.001$ ), predominantly in the responders group. Taken together, a 2006 meta-analysis about the efficacy of MTX in AS concluded that there is no evidence of a beneficial effect in AS, especially for the axial symptoms (Evidence Grade A) (25).

However, the dosages tested in these studies were relatively low compared with those currently used for the treatment of rheumatoid arthritis. To determine whether the lack of evidence of methotrexate for the treatment of ankylosing spondylitis might be due to underdosing, a more recent 16-week open label trial of methotrexate, using a relatively high dose of 20mg subcutaneously per week was performed. This trial did not show any effect on axial and only some non-significant improvements in peripheral symptoms (26).

Therefore, methotrexate is neither recommended for the axial nor for the peripheral manifestations of AS. However, in some patients with predominant peripheral arthritis, a treatment trial might be justified.

#### **Combination therapy with methotrexate**

In contrast to RA, where a combination of methotrexate with other DMARDs is well investigated, it shows synergistic effects and clearly increases the efficacy on signs and symptoms of RA, there are no studies in AS on combination therapies of MTX with other

DMARDs. This is probably because of its inefficacy in monotherapy. There is one open label trial existing comparing sulfasalazine (SSZ), MTX (10mg/week) and its combination in early SpA patients with active sacroiliitis as shown by the short tau inversion recovery technique (STIR) on Magnetic resonance imaging (MRI). This trial demonstrated no statistically significant influence of any of these therapies on active sacroiliitis on MRI, neither on CRP and ESR levels. Clinical outcome parameters were not investigated (27).

Because of the common strategy in RA to combine TNF blockers and MTX, which leads to higher efficacy and safety, this was also investigated in AS.

In the Danish nationwide rheumatological database (DANIBO) register, among other parameters, the use of MTX was investigated regarding disease activity, clinical response, treatment duration and predictors of drug survival (*i.e.* number of days individual patients maintained on treatment) and clinical response among patients with AS receiving their first treatment series with a TNF blocker. In a Cox regression analysis, baseline characteristics associated with longer drug survival included male gender, CRP  $> 14$ mg/l and low visual analogue scale for fatigue, but not the use of MTX, age, or the chosen TNF-blocker (19). Neither effect on clinical efficacy parameters in patients additionally using MTX was found.

In a Norwegian register where drug survival on TNF blockers was investigated in patients with RA, psoriatic arthritis (PsA) and AS, in the RA and PsA patients the additional use of MTX showed a significant influence regarding longer drug survival, but this was not the case in patients with AS (20).

In a clinical trial lasting over one year, the efficacy of continuous treatment with infliximab (IFX) with that of a treatment regimen adapted to symptom recurrence was compared, and MTX was added to test whether this combination could help increase clinical efficacy (28). Patients were randomly assigned to receive IFX every 6 weeks (continuous treatment) or upon symptom recurrence (on-demand treatment),

following infusions at weeks 4, 6, and 10. Patients in the on-demand group were randomly assigned to receive either MTX in combination with IFX or IFX alone. The primary endpoint was the proportion of patients achieving a 20% improvement of the Asesemtns in SpondyloArthritis international Society Criteria (ASAS20) at week 58. A greater proportion of patients receiving IFX continuously achieved ASAS20 than did patients receiving on-demand treatment (75% vs. 46%;  $p < 0.0001$ ). Addition of MTX did not significantly affect the proportion of patients with an ASAS20 response at week 58, nor the number of IFX infusions administered. In another clinical trial, the short-term efficacy and safety of MTX in combination with infliximab was compared with infliximab and placebo in patients with active AS over 22 weeks (29). The authors concluded that a combination of MTX with infliximab is as safe and as effective as infliximab monotherapy in the treatment of AS with a significant improvement in ASAS20 and other outcome parameters including MRI improvements. There was no additional clinical or MRI improvement with the combination of MTX with infliximab in AS.

This is in contrast to a small open label clinical trial from Spain with the aim of assessing the efficacy of IFX combined with MTX versus IFX alone in the treatment of AS over 30 weeks (30). At 14 and 30 weeks, only 50% and 10% respectively of the patients from the IFX group achieved a BASDAI 50 response compared to 89% of patients from the IFX+MTX group ( $p = 0.001$ ) at both time points. In conclusion, in this open label trial with a rather small group of patients, infliximab in combination with MTX, seemed to increase the efficacy of the therapeutic response in active AS patients.

In another trial with 42 patients with AS, in patients treated with MTX infliximab or placebo were added over 22 weeks, and clinical efficacy and time to relapse were investigated (31). Disease flares were reported 8 weeks after the last infusion, indicating that the addition of methotrexate fails to extend the infliximab dosing interval.

## Summary

Taken together, in contrast to RA, methotrexate is not effective for the axial manifestations in AS and might have some effects on peripheral symptoms. Combination of MTX and other DMARDs were not tested in clinical trials in AS, and therefore no statement on efficacy can be given. The combination of MTX and TNF-blockers was tested regarding clinical efficacy, prolongation of dosing interval and drug survival with no additional influence on these outcome parameters, and is therefore not recommended to use in patients with AS.

## References

1. BRAUN J, BOLLOW M, REMLINGER G *et al.*: Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum* 1998; 41: 58-67.
2. JOHNSEN K, GRAN JT, DALE K, HUSBY G: The prevalence of ankylosing spondylitis among Norwegian Samis (Lapps). *J Rheumatol* 1992; 19: 1591-4.
3. SPADARO A, RICCIERI V, SILI-SCAVALLI A *et al.*: Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study. *Clin Exp Rheumatol* 1995; 13: 589-93.
4. BRAUN J, SIEPER J: Ankylosing spondylitis. *Lancet* 2007; 369: 1379-90.
5. VAN DER LINDEN S, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.
6. RUDWALEIT M, KHAN MA, SIEPER J: The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum* 2005; 52: 1000-8.
7. RUDWALEIT M, BRAUN J, SIEPER J: (ASAS classification criteria for axial spondyloarthritis). *Z Rheumatol* 2009; 68: 591-3.
8. BRAUN J, BRANDT J, LISTING J *et al.*: Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002; 359: 1187-93.
9. VAN DER HEIJDE D, DIJKMANS B, GEUSENS P *et al.*: Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (AS-SERT). *Arthritis Rheum* 2005; 52: 582-91.
10. VAN DER HEIJDE D, KIVITZ A, SCHIFF MH *et al.*: Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; 54: 2136-46.
11. DAVIS JC, JR., VAN DER HEIJDE D, BRAUN J *et al.*: Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003; 48: 3230-6.
12. BRANDT J, KHARIOUZOV A, LISTING J *et al.*: Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum* 2003; 48: 1667-75.
13. INMAN RD, DAVIS JC JR, HEIJDE D *et al.*: Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 2008; 58: 3402-12.
14. DOUGADOS M, VAN DER LINDEN S, LEIRIS-ALO-REPO M *et al.*: Sulfasalazine in the treatment of spondylarthropathy. A randomized, multicenter, double-blind, placebo-controlled study. *Arthritis Rheum* 1995; 38: 618-27.
15. CHEN J, LIU C: Sulfasalazine for ankylosing spondylitis. *Cochrane Database Syst Rev* 2005; CD004800.
16. ZOCHLING J, VAN DER HEIJDE D, BURGOS-VARGAS R *et al.*: ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006; 65: 442-52.
17. HEIBERG MS, NORDVAG BY, MIKKELSEN K *et al.*: The comparative effectiveness of tumor necrosis factor-blocking agents in patients with rheumatoid arthritis and patients with ankylosing spondylitis: a six-month, longitudinal, observational, multicenter study. *Arthritis Rheum* 2005; 52: 2506-12.
18. WARD MM, KUZIS S: Medication toxicity among patients with ankylosing spondylitis. *Arthritis Rheum* 2002; 47: 234-41.
19. GLINTBORG B, OSTERGAARD M, KROGH NS *et al.*: Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumor necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. *Ann Rheum Dis* 2010, May 28 [Epub ahead of print].
20. HEIBERG MS, KOLDINGSNES W, MIKKELSEN K *et al.*: The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. *Arthritis Rheum* 2008; 59: 234-40.
21. ALTAN L, BINGOL U, KARAKOC Y *et al.*: Clinical investigation of methotrexate in the treatment of ankylosing spondylitis. *Scand J Rheumatol* 2001; 30: 255-9.
22. ROYCHOWDHURY B, BINDEY-BAGOT S, HUNT T, TUNN E: Methotrexate in severe ankylosing spondylitis - a randomized placebo-controlled study. *Rheumatology* 2001; 40 (Suppl. 1): S43.
23. GONZALEZ-LOPEZ L, GARCIA-GONZALEZ A, VAZQUEZ-DEL-MERCADO M *et al.*: Efficacy of methotrexate in ankylosing spondylitis: a randomized, double blind, placebo controlled trial. *J Rheumatol* 2004; 31: 1568-74.
24. SAMPAIO-BARROS PD, COSTALLAT LT, BERTOLO MB *et al.*: Methotrexate in the treatment of ankylosing spondylitis. *Scand J Rheumatol* 2000; 29: 160-2.
25. CHEN J, LIU C: Methotrexate for ankylosing spondylitis. *Cochrane Database Syst Rev* 2004; CD004524.
26. HAIBEL H, BRANDT HC, SONG IH *et al.*: No efficacy of subcutaneous methotrexate in active ankylosing spondylitis - a 16 weeks open label trial. *Ann Rheum Dis* 2007; 66: 419-21.
27. KABASAKAL Y, KITAPCIOGLU G, YARGUCU

- F *et al.*: Efficacy of SLZ and MTX (alone or combination) on the treatment of active sacroiliitis in early AS. *Rheumatol Int* 2009; 29: 1523-7.
28. BREBAN M, RAVAUD P, CLAUDEPIERRE P *et al.*: No Superiority of Infliximab (INF) + Methotrexate (MTX) over INF Alone in the Treatment of Ankylosing Spondylitis (AS): Results of a One-Year Randomized Prospective Study. *Arthritis Rheum* 2005; 52 (9, Suppl.): S214.
29. LI EK, GRIFFITH JF, LEE VW *et al.*: Short-term efficacy of combination methotrexate and infliximab in patients with ankylosing spondylitis: a clinical and magnetic resonance imaging correlation. *Rheumatology* (Oxford) 2008; 47: 1358-63.
30. PEREZ-GUIJO VC, CRAVO AR, CASTRO MDEL C *et al.*: Increased efficacy of infliximab associated with methotrexate in ankylosing spondylitis. *Joint Bone Spine* 2007; 74: 254-8.
31. MARZO-ORTEGA H, MCGONAGLE D, JARRETT S *et al.*: Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. *Ann Rheum Dis* 2005; 64: 1568-75.