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Should we combine biologics with methotrexate in axial spondyloarthritis?

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1. Introduction

Historically, the benefit of a combination therapy of bDMARDs and methotrexate (MTX) is based on clinical trials and real life experience in patients with rheumatoid arthritis and an inadequate response to MTX, in whom TNF inhibitors and a variety of other bDMARDs were explored initially. Despite the clinical efficacy of bDMARDs and tsDMARDs in monotherapy, the overall benefit of combining these agents with MTX is further supported by the EULAR recommendations for the management of rheumatoid arthritis [[1,2]]. A synergistic mechanism of action and the prevention of the development of drug-neutralizing antibodies seem to favour the combination treatment strategy [2]. Whether this concept can be transferred to the management of other inflammatory diseases such as axial spondylarthropathy, is still under debate.

2. CONS

There are several reasons, why biological disease modifying drug (bDMARD) with methotrexate should not be routinely combined with methotrexate.

Firstly, in contrast to rheumatoid arthritis or psoriatic arthritis, there is no evidence that methotrexate has any meaningful effect on axial or peripheral manifestations of spondyloarthritis (SpA). In a Cochrane review, initially performed in 2004 and updated in 2013, only 3 randomized controlled trials with methotrexate in ankylosing spondylitis (AS, nowadays also referred to as radiographic axial SpA) could be summarized [3,4]. In these trials, methotrexate was applied in rather low dosing regimens (between 7.5 and 10 mg per week) for a time period of 12 to 24 weeks. There was no clinical effect of methotrexate in two of these trials [5,6], while in one study with a higher proportion of patients with peripheral arthritis, a better response in some of the outcome variables was reported [7]. Importantly, none of these studies utilized standardized ASAS (Assessment of Spondyloarthritis International Society) response criteria. In another study not included in the Cochrane review because of the open-label design, methotrexate was given intramuscularly in a dose of 12.5 mg/week for one year to 34 patients with ankylosing spondylitis. The authors considered 53% of the treated patients (most of them with peripheral arthritis) as responders at the end of the treatment period [8], but again, this study did not use standardized ASAS outcome parameters. A higher dose of methotrexate (20 mg/week subcutaneously) has been tested in another open-label study in patients with ankylosing spondylitis – without any effect on axial and only some non-significant improvement of peripheral symptoms [9]. There was also no significant impact of methotrexate given in dose of 10 mg/week (alone or in combination with sulfasalazine) on active sacroiliitis on magnetic resonance imaging in early axial SpA in a further open-label study [10]. It should be concluded, therefore, that the evidence of inefficacy of methotrexate in axial spondyloarthritis comes from studies with a high risk of bias because of design aspects, low-dose of methotrexate applied, short treatment duration, and applied outcome parameters, while a high quality randomized controlled trial with standardized outcome parameters is still missing.

Secondly, addition of methotrexate to a tumour necrosis factor (TNF) α blocker does not appear to improve significantly clinical or MRI response as compared to a TNF blocker monotherapy in patients with axial SpA [11–13]. There is only one small open-label study in AS, which could show some increase in treatment response to infliximab associated with methotrexate [14]. Also, no influence of methotrexate of pharmacokinetics and pharmacodynamics of TNF blockers in AS including and no clear impact on anti-drug antibody formation could be found [15,16]. It should be mentioned, however, that the same limitations as mentioned above regarding study design, dosing regimen and duration of the study do apply also here.

And finally, there are no convincing data that methotrexate is able to improve a long-term survival of bDMARDs in axial SpA (though data are available for TNF blockers only). In observational studies DANBIO, NOR-DMARD and most recently also in the Portuguese Register, use of methotrexate was not associated with a better survival of TNF α blockers in AS over up to 13 years of observation and no clear additional clinical effect of methotrexate could be shown [17–19]. Some positive effect of methotrexate on drug survival was observed, however, in the Swedish National Biologics Register (ARTIS) [20] and in the Swiss Clinical Quality Management Cohort (SCQM) [21]; in the latter

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study, the positive effect of methotrexate on TNF blocker survival was attributable mostly to infliximab – the most immunogenic TNF blocker. Of note, TNF α blocker survival is generally better in axial SpA (and to a further extent, also in psoriatic arthritis) than in rheumatoid arthritis [17].

Thus, taking the available data together, there is almost no evidence that methotrexate has any effect on manifestations of SpA alone or in combination with bDMARDs. The level of evidence is, however, low, well-designed clinical trials are necessary in order to answer the question, if and in which patients an addition of methotrexate to a bDMARD might improve an outcome in axial SpA.

3. Pros

Patients with spondyloarthropathies manifest notable clinical responses with bDMARDs therapy [22–25]; yet inhibition of radiographic progression in these patients following blockage of TNFα or IL-17 still seems to be a challenging goal to be achieved [26,27]. In contrast to the rapid clinical response to bDMARDs, their inhibitory effects of on axial radiographic progression appears only following several years of continuous therapy [28]. Interestingly, continuous daily nonsteroidal therapy (NSAID) has been shown to inhibit radiographic axial progression in ankylosing spondylitis patients; daily therapy with celecoxib ranging 100 mg to 200 mg twice daily (or another NSAID as long as they maintained the same treatment strategy) was found to be superior to an on-demand approach. Despite these promising results such a therapeutic regime was not commonly adopted given the NSAIDS's deleterios cardiovascular and renal effects [29]. A need therefore to augment the clinical and readiogropahic impacts of bDMARDs still remains nowadays as an unmet need.

Several reports have shown that cDMARDS do not provide such a contribution, but have we appropriately assessd thier contribution or have we discarded interesting findings prematurely?

The ESTHER study, which was a comparative study of sulfasalazine versus etanercept in early axial spondyloarthropathies, targeted MRI sacroiliac joint scores. While the mean MRI sacroiliac joint score declined by 69.2% among those treated with etanercept, a parallel decline of 35.2% was measured among the sulfasalazine treated patients. The ESTHER study design did not include a placebo group so it cannot be clearly determined if sulfasalazine provided any true benefit, but on the other hand one cannot exclude any favorable impact at least in selected patients, especially as the improvement by an objective score was not negligible [30].

Lessons regarding the advantages of combining of bDMARDs with cDMARDs have been long ago learned with the use of bDMARDs and cDMARDs in rheumatoid arthritis (RA) patients. Both the TEMPO and the PREMIER studies have shown synergistic outcomes by combining either etanercept or adalimumab with methotrexate, these outcomes were chosen as the primary outcomes in these studies [31,32]. Yet there were no large randomized, double blinded studies in patients with spondyloarthropathies that were designed to clarify this issue and the data that we rely originate from secondary outcomes of various limited scale studies.

Another leading concept favouring combination arises from the observation that was thoroughly investigated in RA patients, that comedication reduces the titers of neutralizing antibodies directed against anti-TNFα agents [33,34]. Why should we assume that this concept is irrelevant in patients with spondyloarthropathies? Has it been appropriately addressed?

Several reports have shown that in contrast to the prevalent belief, there are indeed high levels of anti-drug antibodies appearing in patients with spondyloarthropathies treated with TNFα inhibitors ranging from 0.04%–31% of the patients assessed [35].

In an Israeli study of 93 patients with psoriatic arthritis (PsA), 48 receiving adalimumab, 24 infliximab, and 21 etanercept, high levels of anti-drug antibodies were detected in 29%, 21% and 0% respectively. Anti-drug antibodies significantly correlated with lower drug levels, higher 28-joint Disease Activity Scores (DAS28) and higher global assessments. Interestingly methotrexate comedication significantly correlated with a lower prevalence of anti-drug antibodies [36]. While some studies showing no added value of comedication of adalimumab and methotrexate [37] a prospective study combining cyclosporine with adalimumab had provided promising articular and cutaneous outcomes from each arm of monotherapy, yet this study was not blinded nor randomized [38].

Another study assessing the efficacy of infliximab in patients with PsA have shown at week 66 that 15.4% of the patients in the combined infliximab methotrexate group were positive for antibodies to infliximab; most had low antibody titers. While only 3.6% of patients receiving MTX at baseline were positive for antibodies to infliximab, 26.1% of those not receiving MTX at baseline tested positive. Although the study was not aimed for this purpose, these findings probably may have an impact on the duration of drug survival, which is extremely important, given the relatively young age of patients diagnosed with spondyloarthropathies and their need for many years of bDMARDs therapy [39].

Despite several negative reports regarding comedication of anti-TNFα outcomes with methotrexate the Respond trial was an open-labeled study of 115 patients with active PsA who were naive to methotrexate and other cDMARDS. The trial assignment was to either infliximab and methotrexate or to methotrexate alone at a 1:1 ratio. The study compared the ACR20 responses at week 16 as a primary outcome and psoriasis area and severity index (PASI), DAS28, dactylitis and enthesitis assessments as secondary outcomes. At week 16, 86.3% of patients receiving infliximab plus methotrexate and 66.7% of those receiving methotrexate alone achieved an ACR20 response ($p < 0.02$). Of patients whose baseline PASI was 2.5 or greater, 97.1% receiving infliximab plus methotrexate compared with 54.3% receiving methotrexate alone experienced a 75% or greater improvement in PASI ($p < 0.0001$). Improvements in C-reactive protein levels, DAS28 responses and remission rates, dactylitis, fatigue and morning stiffness duration were also significantly greater in the comedication group. A recent study that compared etanercept or methotrexate monotherapies with comedication showed greater efficacy of either etanercept alone or as comedication [40]. Yet there was no benefit of combining the medications in comparison monotherapy with etanercept.

However, an analysis of the Norwegian longitudinal observational study on disease-modifying antirheumatic drugs (NOR-DMARD) had compared patients with PsA starting their first TNF inhibitor, either as monotherapy or with concomitant methotrexate. Of the 440 patients included 170 received a TNF inhibitor as monotherapy and 270 concomitant methotrexate. Responses were similar in the two groups in both analyses. Drug survival analyses revealed a borderline significant difference in favour of patients receiving comedication ($p = 0.07$), and this was most prominent for patients receiving infliximab (IFX) ($p = 0.01$). In the Cox regression analysis lack of concomitant methotrexate and current smoking were independent predictors of discontinuation of TNF inhibitors [41].

We may conclude in admitting that insufficient attention has been paid throughout the years regarding the optimal regimen of bDMARDS. This issue has not been properly addressed in the major clinical studies nor had the best cDMARDS agent for comedication been determined. Interesting findings suggest that cyclosporine may be a proper candidate for comedication with TNF inhibitors. It seems that comedication may prevent the generation of anti-drug antibodies in patients with spondyloarthropathies, similarly to their effect in patients with RA. Utilizing such an approach may prolong the bDMARDS drug survival in patients with spondyloarthropathies.

Declaration of Competing Interest

DP: research grants from Abbvie, MSD, Novartis, Pfizer;

consultancy/speaker fees from: Abbvie, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, UCB.

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