Disease-modifying Antirheumatic Drugs (DMARD) and Combination Therapy of Conventional DMARD in Patients with Spondyloarthritis and Psoriatic Arthritis with Axial Involvement

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ABSTRACT. Treatment with nonsteroidal antiinflammatory drugs (NSAID) is the recommended first-line therapy in patients with axial spondyloarthritis (axSpA); and for those patients who have persistently active disease, the introduction of tumor necrosis factor-α (TNF-α) inhibitors is indicated. Conventional nonbiological disease-modifying antirheumatic drugs (DMARD), although effective and used in clinical practice for peripheral arthritis, are not recommended. Few studies have been conducted with the aim of evaluating the effect of conventional DMARD, either alone or in combination, in axSpA. As for psoriatic arthritis (PsA), DMARD are widely used, but few trials are available about their effects on axial involvement, which is not often assessed as a primary outcome in clinical trials. In rheumatoid arthritis, combination therapy of 2 or more conventional DMARD appears to confer better response than methotrexate monotherapy, and may even be a viable alternative to TNF-α inhibitors. In peripheral PsA, combination therapy can be used after treatment failure with 1 DMARD, but few studies have been conducted. However, available evidence for the combination of conventional DMARD indicates a lack of any significant benefit on axial symptoms; thus this treatment approach does not represent an effective alternative to anti-TNF-α therapy. (J Rheumatol Suppl. 2015 Nov;93:65–9; doi:10.3899/jrheum.150640)

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The spondyloarthritides are a group of conditions characterized by clinical manifestations such as inflammatory back pain, arthritis, and enthesitis, and an association with HLA-B27, and the presence of sacroiliitis on radiographic imaging. These conditions, with typical onset at young age, can result in severe disability and increased morbidity during what are normally the most productive years of life.

The Assessment of Spondyloarthritis International Society (ASAS) has produced classification criteria for spondyloarthritides (SpA) whose principal clinical involvement is the axial skeleton, introducing the term axial SpA (axSpA). The criteria also cover patients with radiographic sacroiliitis, termed ankylosing spondylitis (AS), and patients before the occurrence of structural damage visible on radiographic imaging, now termed nonradiographic (nr)-axSpA[1].

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Despite sharing several clinical features and a similar disease activity burden with AS and axSpA in general, axial disease in psoriatic arthritis (PsA) presents specific characteristics such as less overall spinal disease severity, asymmetric and less-severe sacroiliitis, asymmetric distribution of marginal and paramarginal syndesmophytes, and a weaker association with the HLA-B27[2]. According to the ASAS classification criteria, certain patients with axial psoriatic arthritis (axPsA) can also be classified within axSpA.

Nonsteroidal antiinflammatory drugs (NSAID) have been accepted as an effective first-line therapy in axSpA; however, for those patients who do not tolerate NSAID or whose response is insufficient to control disease activity, anti-tumor necrosis factor-α (TNF-α) agents are recommended[3]. In axPsA, although outcomes concerning axial disease are not often specified as endpoints in randomized clinical trials (RCT) of anti-TNF-α, significant benefits have been noted with these drugs, both in monotherapy and in combination with DMARD; consequently, for the treatment of axPsA, physicians often refer to recommendations for AS.

Anti-TNF-α therapy is clinically effective in AS, nr-axSpA, and axPsA, but the costs of treatment are not negligible, and there is controversy regarding the effects on radiographic progression of disease.

DMARD in AxSpA and PsA with Axial Involvement

The efficacy of nonbiological DMARD in axSpA is controversial: for years they have been considered a second-line approach for patients refractory to or intolerant of NSAID, but there is insufficient evidence of their efficacy, and they have been investigated in only a limited number of studies in axial disease.

Sulfasalazine. Sulfasalazine (SSZ) is a DMARD that has long been used to treat patients with AS, but few studies have been conducted. A large placebo-controlled study showed improvement in peripheral joint disease in SpA, whereas no effect was seen on axial symptoms[4]. Braun, *et al*[5] found that SSZ was no better than placebo overall on inflammatory low back pain in patients with undifferentiated SpA or AS. In a double-blind RCT versus etanercept (ETN; ASCEND trial)[6], the proportion of responders according to the ASAS20[7] was higher with ETN, but SSZ showed some efficacy. Similarly, in a RCT comparing ETN to SSZ in early axSpA (ESTHER trial), the anti-TNF outperformed SSZ, but a certain degree of benefit was shown also with the conventional treatment, as shown by the percentage of patients achieving ASAS20, ASAS40, and ASAS-partial remission; however, very scarce improvement of the MRI score was observed in patients receiving SSZ[8]. Today, the most recent ASAS/European League Against Rheumatism (EULAR) recommendations in the treatment of AS suggest that SSZ could be used in patients with peripheral arthritis who do not respond to NSAID before switching them to anti-TNF-α therapies[3].

The evidence for methotrexate (MTX) is more limited. Although used extensively in rheumatoid arthritis (RA), MTX was demonstrated to be ineffective in active AS in an open-label trial[9] in which only 25% of patients achieved ASAS20 response. Other controlled trials showed conflicting results, but a recent metaanalysis in patients with AS found MTX to have limited to no effect on both axial and peripheral disease[10].

On the other hand, in PsA, DMARD are considered effective and are widely in use. The EULAR recommendations[11] state that patients who have active disease despite previous NSAID therapy or with poor prognostic features should receive a synthetic DMARD, chosen from those with the best evidence for efficacy [MTX, leflunomide (LEF), and SSZ], with MTX to be considered the first-choice DMARD. As shown in RA trials, LEF has clearly been demonstrated to be statistically highly significantly more efficacious in peripheral PsA compared to placebo[12]. Small retrospective studies have confirmed the efficacy of LEF in clinical practice[13]. Despite the lack of strong trials, LEF is commonly used in PsA in clinical practice.

The number of studies with synthetic DMARD is limited, but the evidence is that their real efficacy is limited. Moreover, these drugs do not appear to be efficacious for treating enthesitis and axial disease in PsA. Axial disease, in particular, is rarely assessed in clinical trials for PsA, which are more frequently performed in patients with polyarticular joint involvement.

Corticosteroids. Although corticosteroids do not fall under the definition of DMARD, they may provide rapid relief for axial symptoms; but oral administration at conventional doses is of little value; recently, in a double-blind placebo-controlled trial in patients with active AS, only oral prednisolone 50 mg per day, and not low-dose prednisolone, showed a short-term response that was significantly higher than placebo[14].

Combination Therapy of DMARD in AxSpA and PsA

Surprisingly, studies analyzing combination therapy using conventional nonbiological drugs in SpA are scarce. In RA, a strategy of combining DMARD and prednisolone, targeted to decrease disease activity immediately after diagnosis, proved to have favorable effects on disease activity and radiographic joint damage progression. This combination proved to be superior to monotherapy for suppressing disease activity, and these effects were sustained after longterm followup. This was observed in the COBRA trial (COmbinatietherapie Bij Reumatoide Artritis) in which patients were treated with SSZ, MTX, and initial high-dose prednisolone (60 mg/day)[15]. Subsequent studies demonstrated that COBRA therapy was as effective as combination therapy with MTX and initial anti-TNF-α treatment (infliximab), and was even superior to initial monotherapy with MTX and stepup therapy in the first months of treatment[16]. These data indicate that combination therapy leads to the same results as an anti-TNF–α therapy, thus suggesting that the target (TNF-α and the downstream inflammatory effects) should be controlled at the same level. Yet no similar data from RCT are available in SpA or PsA.

The combination of conventional DMARD in PsA has been attempted in few studies: in a 12-month RCT in incomplete responders to MTX[17], the combination of MTX plus cyclosporine (CSA) provided clearcut clinical improvement as well as ultrasound improvement, suggesting that combination therapy is better than MTX monotherapy. Clinical improvement in treatment with CSA was similarly confirmed in a previous multicenter trial that compared SSZ to CSA in PsA. Indeed, CSA showed benefits at least comparable to or greater than SSZ in peripheral PsA, and more importantly, showed statistically significantly better results according to the Bath Ankylosing Functional Index[18] in the subset with axial involvement[19].

The better efficacy of triple combination therapy of MTX + SSZ + hydroxychloroquine versus monotherapy (SSZ) and double therapy (SSZ + MTX) was confirmed in an uncontrolled study in peripheral PsA by Çalguneri, *et al*[20]. These data show that combination therapy works better than monotherapy with SSZ in peripheral PsA, and CSA provides some benefit in axPsA.

In axSpA, the combination of conventional DMARD has

been evaluated in even fewer studies. In a retrospective study[21], the efficacy of mono- and combination therapy with MTX and SSZ in patients with AS was evaluated: a significant subset of patients responded to SSZ + MTX combination or to SSZ monotherapy.

In a previously unpublished, prospective proof-of-concept study, we aimed to evaluate the efficacy of combined treatment with SSZ, MTX, and initial high-dose steroid in a cohort of patients with axSpA who failed NSAID therapy (mostly naproxen 1 g/day) for 1 month. The aim was to see whether a majority of patients would respond and how many would require anti-TNF-α therapy after at least 3 months of treatment. We prospectively enrolled 10 patients with diagnosis of axSpA according to ASAS classification criteria, with active disease [Bath Ankylosing Arthritis Disease Activity Index[22] (BASDAI) ≥ 4)] attending the rheumatology division of our center. All patients had evidence of axSpA on magnetic resonance imaging, with involvement of 1 or 2 sacroiliac joints along with other extraarticular sites (vertebral osteitis, longitudinal tendons, etc.). Two patients had active skin psoriasis at the time of enrollment. The patients were treated with a combination of SSZ (2 g/day) + MTX (10–20 mg/week) and oral corticosteroid (0.5–1 mg/kg/day) of prednisone with a dosage tapering to reach 7.5 mg/day within 7 weeks then followed only by the NSAID (preferentially naproxen 1 g/day). Disease activity was assessed at baseline, and every 3 months of treatment, by BASDAI, AS Disease Activity Score-C-reactive protein (DAS-CRP) and AS DAS-erythrocyte sedimentation rate (ESR). We also assessed acute-phase reactants (CRP and ESR) and BASFI, and evaluated the requirement for anti-TNF-α therapy in patients who showed persistent symptoms or with BASDAI score ≥ 4 during treatment. All patients with axSpA were treated with combination therapy for at least 3 months. After that period, BASDAI score was not decreased (6.1 ± 1.4 at baseline vs 5.8 ± 0.7 after 3-month followup; p = 0.40) and no patient reached a low disease activity state (BASDAI < 4). ESR was significantly decreased after 3 months of followup (38.7 ± 25.9 at baseline vs 12.7 ± 11.3 mm/h after 3 mos followup; p = 0.01) whereas CRP showed no significant change after 3 months of combination treatment (p = 0.24). Two patients showed improvement in the AS DAS-ESR and the AS DAS-CRP scores (Δ ≥ 1.1; Figure 1). All patients continued treatment for a mean period of 5.6 months, with 12 months being the last patient survival of the treatment protocol. Between the sixth and 12th month, 7 patients had to be switched to anti-TNF-α treatment, while 1 was lost at the followup visit. The other 2 continued combination therapy with a certain degree of clinical improvement, but did not reach a state of low disease activity.

DISCUSSION

Monotherapies with drugs that are efficacious in RA have been shown to provide clinical benefits; although not efficacious in all studies in SpA, they are effective in PsA overall. Combination therapies with conventional DMARD allowed rescue of a proportion of patients who were incomplete responders to MTX (or SSZ), but again almost all in peripheral arthritis. Except for CSA, no other DMARD has provided benefit in axial manifestations.

With combination therapy of SSZ, MTX, and oral high-dose corticosteroid, a therapeutic approach considered effective for RA, we aimed to clarify whether this therapy could spare the use of biologics, as a second-line treatment for patients with axial symptoms who showed no clinical improvement with NSAID. Despite the low number of patients and the lack of a control group, it can be concluded that combination therapy of corticosteroids, MTX, and SSZ does not appear to be an effective option for these patients, failing to control disease activity or delay the use of anti-TNF-α agents. It is also likely that in patients with longer disease duration, even worse results are to be expected. Combination treatment appeared to be ineffective on axial symptoms, similarly to treatment with a single DMARD, none of which is currently recommended for treatment of AS and axSpA, with the exception of SSZ in patients with peripheral arthritis.

Treatments for axPsA have not specifically been studied, and very few data are available on traditional therapies. Moreover, in RCT of PsA, improvement in axial disease is not often specified as an endpoint, and outcome measures originally developed for AS are used; thus, response to therapy is assumed to be equivalent between AS and axPsA. By extension, since traditional oral DMARD have not been shown to be effective in axSpA, they are not considered to be of adequate efficacy for axPsA[23].

Nevertheless, the presence of side effects and the high costs of anti-TNF-α agents are elements to be considered when seeking to identify a viable alternative to biological drugs. While novel agents are being investigated, further trials are warranted, especially for patients in the very early phases of disease in the nr-axSpA phase, to clarify whether real alternatives to TNF-α inhibitors exist in the very early phases of disease; in which case, the nonradiographic stage could really be considered the "window of opportunity" in SpA disease.

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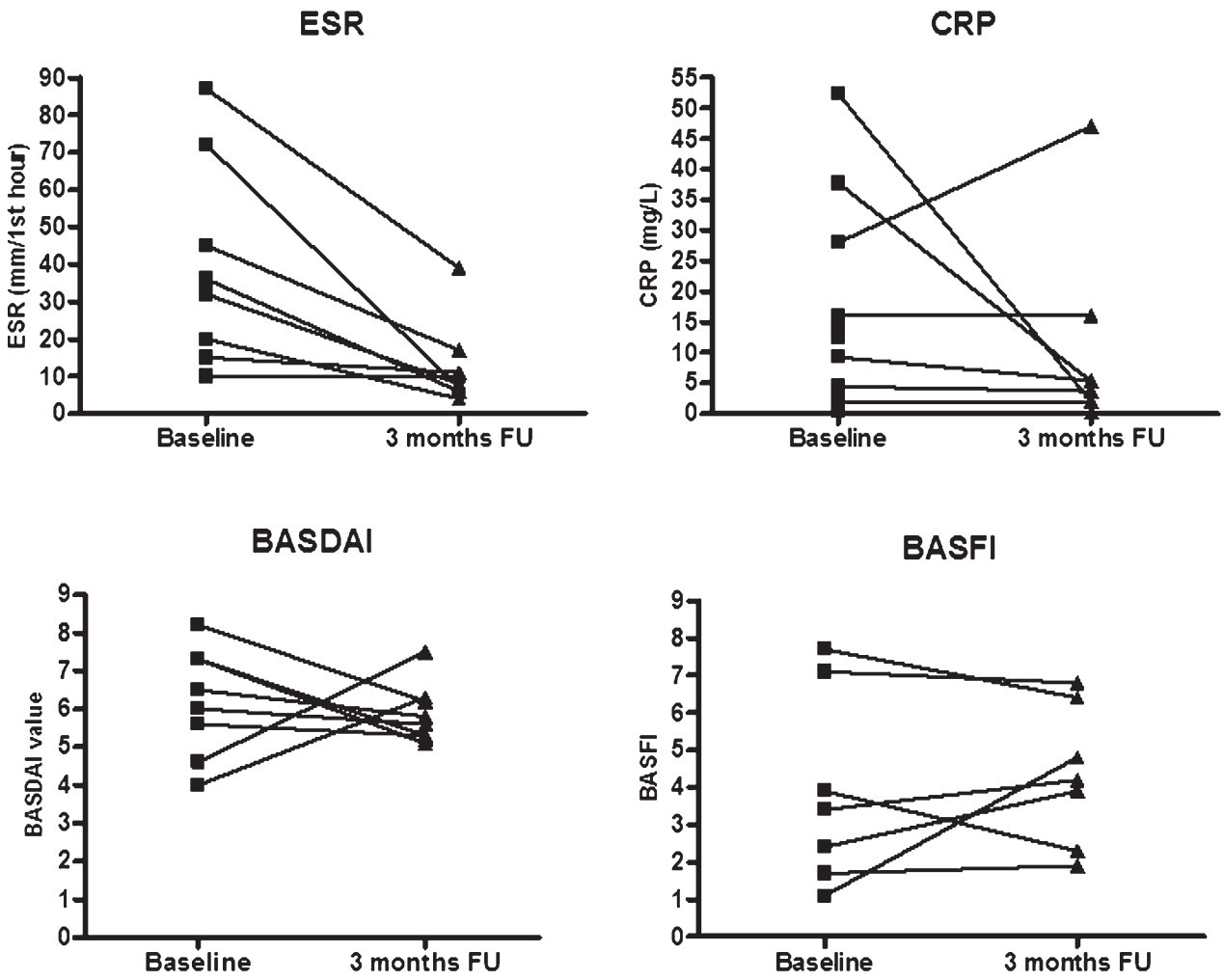

Figure 1. Individual changes in laboratory and clinimetric variables at baseline and after 3-month followup during combination therapy in patients with axial spondyloarthritis. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; FU: followup.

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