CONCISE REPORT

Treating axial and peripheral spondyloarthritis, including psoriatic arthritis, to target: results of a systematic literature search to support an international treat-to-target recommendation in spondyloarthritis

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ABSTRACT

Background Current recommendations for the management of axial spondyloarthritis (SpA) and psoriatic arthritis are to monitor disease activity and adjust therapy accordingly. However, treatment targets and timeframes of change have not been defined. An international expert panel has been convened to develop ‘treat-to-target’ recommendations, based on published evidence and expert opinion.

Objective To review evidence on targeted treatment for axial and peripheral SpA, as well as for psoriatic skin disease.

Methods We performed a systematic literature search covering Medline, Embase and Cochrane, conference abstracts and studies in http://www.clinicaltrials.gov.

Results Randomised comparisons of targeted versus routine treatment are lacking. Some studies implemented treatment targets before escalating therapy: in ankylosing spondylitis, most trials used a decrease in Bath Ankylosing Spondylitis Disease Activity Index; in psoriatic arthritis, protocols primarily considered a reduction in swollen and tender joints; in psoriasis, the Modified Psoriasis Severity Score and the Psoriasis Area and Severity Index were used. Complementary evidence correlating these factors with function and radiographic damage at follow-up is sparse and equivocal.

Conclusions There is a need for randomised trials that investigate the value of treat-to-target recommendations in SpA and psoriasis. Several trials have used thresholds of disease activity measures to guide treatment decisions. However, evidence on the effect of these data on long-term outcome is scarce. The search data informed the expert committee regarding the formulation of recommendations and a research agenda.

INTRODUCTION

Recommendations from the Ankylosing Spondylitis Assessment Study (ASAS)/European League Against Rheumatism (EULAR) for the management of ankylosing spondylitis (AS)1, 2 and from EULAR for the management of psoriatic arthritis (PsA)2 are to monitor the disease,1, 2 adjust treatment appropriately,2 and adapt the frequency of monitoring depending on the course and severity of the disease.3 However, no evidence that a guided treatment strategy is as effective for AS and PsA as it is for rheumatoid arthritis (RA)4 has yet been established. This is partly due to the heterogeneity of the presentations of these and related diseases, which some would group under the broader term, spondyloarthritis (SpA). In fact, it has been suggested that the terms axial SpA and peripheral SpA could be considered rather than the traditional names.5 To address this issue, an international panel of expert rheumatologists and patients convened to discuss recommendations on a ‘treat-to-target’ (T2T) concept for SpA. In line with respective recommendations by EULAR,6 a systematic literature review of the current state of evidence was deemed necessary. In the following, we present this systematic literature review, which served as the background for generating the recommendations document.6

METHODS

We performed a systematic literature search of the Medline, Embase and Cochrane databases. This search was based on a PICO (population, intervention, control and outcome) strategy and search terms developed in the course of discussions of the task force’s steering committee. Box 1 shows the PICO strategy, and online supplementary table S1 lists the search terms.

We retrieved publications from each database’s inception to September 2011. We also screened 2010 and 2011 EULAR and American College of Rheumatology (ACR) conference abstracts7, 8 and accessed the US National Institutes of Health (NIH) database on clinical trials.9 We selected eligible studies according to our inclusion criteria (see box 1 and online supplementary table S1) and compiled the applied measures of disease activity and the thresholds and timelines that guided the decision to change therapy in the respective study protocols. The primary aim of the search was retrieval of strategic studies that compared a therapy steered towards a prespecified treatment
Box 1 PICO strategy

**Population:** adult patients with axial or peripheral SpA or psoriasis  
**Intervention:** targeted use of NSAIDs, synthetic DMARDs or biologicals  
**Control:** routine treatment  
**Outcome:** the applied definition of a therapeutic target; parameters of disease activity that serve as surrogates for clinical, functional or radiographic success  
**Design:** ‘strategy trial’: interventional, prescheduled therapeutic adaptation; RCT, open-label controlled, or single-arm study  
**Duration:** any given follow-up

Excluded:  
- DX: degenerative and dialysis-associated SpA, psoriasis, spondyloarthritis  
- TX: intervention other than drugs (surgery, physiotherapy, balneotherapy, hydrotherapy, exercise, radon, cryotherapy, mud bath), excluded drugs (bisphosphonates, antidepressants, complementary and alternative medicine (CAM)) and excluded applications (intra-articular injections, intravascular steroids)  
- Study setting: non-interventional (ie, observational/retrospective)  
- Publication form: letters, editorials, narrative reviews

CAM, DMARD, disease-modifying antirheumatic drug; DX, diagnosis; NSAID, non-steroidal anti-inflammatory drug; RCT, randomised controlled trial; PICO, population, intervention, control, outcome; SpA, spondyloarthritis; TX, treatment.

lists details of the included studies and baseline characteristics of the patients.

Definitions of treatment targets and timelines
The majority of studies used the Bath AS Disease Activity Index (BASDAI) at follow-up for treatment ‘escalation’ until a prespecified outcome was achieved.12 15 17 18 This outcome was defined as BASDAI <3 at two consecutive assessments starting from weeks 30 and 36 in one trial,12 while in most studies, a percentage reduction from baseline was required, being either ≥20% after 12 weeks,17 ≥40% after 14 weeks18 or ≥50% after 6 months.15 17 Two protocols required a decline of ≥20%11 or ≥40%14 in the response criteria of the ASAS after 12 weeks. One study13 based treatment decisions on the erythrocyte sedimentation rate (ESR) at follow-up and required a ≥1 mm reduction per week. One trial that included AS and PsA patients required a ≥40% reduction in patient global assessment of disease activity (PGA) after 14 weeks, otherwise infliximab (IFX) frequency was increased from an 8-weekly to a 4-weekly schedule (table 1).

Several authors combined targets, mostly combinations of the BASDAI19 22 or the Bath AS Metrology Index (BASMIX)24 with either acute phase reactants19 23 or the physician global assessment (PhysGA).24 Meric et al16 measured serum IFX levels after four infusions to customise infusion schedules previously determined according to the BASDAI. Reductions in morning stiffness and pain were used to adjust golimumab therapy13 and—expanded by the ESR—also to guide dose escalations of mesalazine.20 Cheung et al22 reported therapeutic outcomes using Australian Pharmaceutical Benefit Schedule standards, which only reinforce ‘continuation’ of IFX after decline of BASDAI by ≥2 points and ≥20% improvement in ESR and/or C-reactive protein (CRP) (table 1). Several studies tested the efficacy of ‘on-demand’ treatment in the case of relapse after cessation of IFX.22 24 The definition of relapse was based on a short questionnaire in combination with BASDAI and an increase in acute phase reactants (table 1).23 or an absolute BASMI or PhysGA of ≥4.24 Therapy was tapered according to ESR,23 BASDAI and serum IFX levels16 (table 1).

In AS, prospective analyses to identify the predictive value of the above measures for long-term functional and radiographic outcomes have not been carried out.

Psoriatic arthritis
Seven studies fulfilled our inclusion criteria for PsA.18 19 25–29 Table 1 details their treatment targets. Online supplementary table S2 shows study details and patients’ baseline characteristics.

In the majority, the treatment target was a reduction in swollen and tender joint counts.26–29 The prespecified decrease for a treatment to be considered sufficiently effective was a reduction in joint counts of ≥10% after 16 weeks,26 ≥20% after 38 and 46 weeks,27 29 ≥30% after 14 weeks28 or ≥40% after 3 months.29 Two trials18 19 included mixed SpA populations and used ≥40% reduction in PGA after 14 weeks18 or ESR and CRP18 (table 1). Some prospective studies investigated the correlation between clinical symptoms and progression of radiographic damage and reported a predictive capacity of synovitis,10–12 dactylitis13 and CRP14 while other authors did not observe these associations.15 Serological markers that can predict long-term outcome in PsA are under investigation.36

There were no trials available that specifically investigated targeted treatment in other peripheral SpAs or contributed evidence on correlation with long-term outcomes.
Clinical and epidemiological research

<p>| Table 1 Treatment targets and timeline definition in trials of ankylosing spondylitis and psoriatic arthritis |</p>
<table>
<thead>
<tr>
<th>Measure of disease activity</th>
<th>Target definition</th>
<th>Assessment after</th>
<th>Study (drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ankylosing spondylitis</strong></td>
<td></td>
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<tr>
<td>ASAS</td>
<td>≥20% response</td>
<td>Week 12 (OLE)</td>
<td>ATLAS (ADA)⁴¹†</td>
</tr>
<tr>
<td>BASDAI</td>
<td>&lt;3 at both current and prior assessment</td>
<td>Week 36</td>
<td>ASSERT (IFX)¹²</td>
</tr>
<tr>
<td>ASAS</td>
<td>≥40% response</td>
<td>Week 12</td>
<td>Haibel (ADA)⁴⁴ †</td>
</tr>
<tr>
<td>BASDAI</td>
<td>≥50% reduction, or ≤3</td>
<td>Week 22 and 38</td>
<td>CANDLE (IFX)¹⁵</td>
</tr>
<tr>
<td>BASDAI</td>
<td>≥20% reduction</td>
<td>Month 3</td>
<td>Jans (IFX)¹⁷</td>
</tr>
<tr>
<td>BASDAI</td>
<td>≥50% reduction</td>
<td>Month 6</td>
<td></td>
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<tr>
<td>ESR</td>
<td>≥40% reduction</td>
<td>Week 14</td>
<td></td>
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<tr>
<td></td>
<td>≥1 mm reduction per week: escalate</td>
<td>Weekly for escalation</td>
<td></td>
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<tr>
<td></td>
<td>≤20 (women) ≤10 (men) mm/h for step down</td>
<td>Month 6 for step down</td>
<td></td>
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<tr>
<td>Combined/alternative targets</td>
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<tr>
<td>Total back pain (VAS), MST (min)</td>
<td>≥20% reduction in both back pain and MST</td>
<td>Week 16</td>
<td>GO-RAISE (GOL)¹³</td>
</tr>
<tr>
<td>BASDAI, IFX serum level</td>
<td>&lt;40 and 5.0 μg/ml</td>
<td>After 4th IFX (~22 weeks)</td>
<td>Meric (IFX)¹⁶</td>
</tr>
<tr>
<td>BASDAI, ESR/CRP</td>
<td>≤3 (BASDAI) or &lt;30 mm/h ESR and &lt;5 mg/l CRP</td>
<td>Week 38</td>
<td>Collantes (IFX)¹⁹</td>
</tr>
<tr>
<td>MST (VAS), pain (VAS), ESR</td>
<td>≥20% reduction in 2/3</td>
<td>Week 4</td>
<td>Van Denderen (mesalazine)²°</td>
</tr>
<tr>
<td>BASDAI, ESR/CRP</td>
<td>≥2 patients. BASDAI reduction and ≥20% ESR/CRP reduction</td>
<td>Week 2, then 6-weekly</td>
<td>Cheung (IFX)²²</td>
</tr>
<tr>
<td>Q1: disease has remained under control?</td>
<td>No relapse: definition:</td>
<td>≥4 weeks after stopping for on-demand</td>
<td>Breban (IFX)²³</td>
</tr>
<tr>
<td></td>
<td>Q1 ‘Yes’ and Q2 ‘No’ and either</td>
<td></td>
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<tr>
<td></td>
<td>≤2/10 pain increase and ≤1/10 BASDAI increase</td>
<td>week 40 for dose escalation</td>
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<tr>
<td>BASMI, PhysGA</td>
<td>No relapse: definition: ≤4 BASMI and ≤4 PhysGA</td>
<td>26 weeks after stop</td>
<td>Braun (IFX)²⁴</td>
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<tr>
<td><strong>Psoriatic arthritis</strong></td>
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<tr>
<td>TJC and SJC</td>
<td>≥20% reduction</td>
<td>12 weeks</td>
<td>ADEPT (ADA)²⁵</td>
</tr>
<tr>
<td>TJC and SJC</td>
<td>≥10% reduction</td>
<td>16 weeks</td>
<td>GO-REVEAL (GOL)²⁶</td>
</tr>
<tr>
<td>TJC and SJC combined N</td>
<td>≥20% reduction</td>
<td>38 and 46 weeks</td>
<td>IMPACT 2 (IFX)²⁷</td>
</tr>
<tr>
<td>Joint count ‘actively inflamed’</td>
<td>≥30% reduction</td>
<td>14 weeks</td>
<td>Feletar (IFX)²⁸</td>
</tr>
<tr>
<td>Joint count</td>
<td>≥40% reduction</td>
<td>3 months</td>
<td>Rahman (SSZ)²⁹</td>
</tr>
<tr>
<td>PGA</td>
<td>≥40% reduction</td>
<td>14 weeks</td>
<td>Cheuvront (IFX)³⁰</td>
</tr>
<tr>
<td>BASDAI, ESR/CRP</td>
<td>≤3 (BASDAI) or &lt;30 mm/h ESR and &lt;5 mg/l CRP</td>
<td>Week 38 (cave diff AB 30/hex38)</td>
<td>Collantes (IFX)³¹</td>
</tr>
<tr>
<td><strong>Psoriasis</strong></td>
<td></td>
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<tr>
<td>MPSS</td>
<td>MPSS&lt;sub&gt;present&lt;/sub&gt; visit – MPSS&lt;sub&gt;previous&lt;/sub&gt; visit ≥0.2* (MPSS&lt;sub&gt;previous&lt;/sub&gt; visit – MPSS&lt;sub&gt;baseline&lt;/sub&gt;)</td>
<td>Max 18 weeks</td>
<td>De Jong (MTX)³²</td>
</tr>
<tr>
<td>PASI</td>
<td>Improvement ≥25%</td>
<td>6 weeks</td>
<td>Beissert (CSA, MMF)³³</td>
</tr>
<tr>
<td>PASI</td>
<td>Improvement ≥75%</td>
<td>12 weeks</td>
<td>Nevin (CSA)³⁴</td>
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</tbody>
</table>

*Target measure is identical with primary end point measure.
†Target measure is not identical with primary end point measure.

ADA, adalimumab; ADEPT, Adalimumab Effectiveness in Psoriatic Arthritis Trial; ASAS, Ankylosing Spondylitis Assessment Study; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASG, Bath Ankylosing Spondylitis Global Score; BASMI, Bath Ankylosing Spondylitis Metrology Index; C-reactive protein; CSA, ciclosporin; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; GOL, golimumab; IFX, infliximab; IFX, immunosuppressant therapy (consisting of combined DMARDs); mesal, mesalazine; MMF, mycophenolate mofetil; MPSS, Modified Psoriasis Severity Score; MST, morning stiffness; MTX, methotrexate; OLE, open label extension; PASI, Psoriasis Area Severity Index; PGA, Patient global assessment of disease activity; PhysGA, physician global assessment; Q1, Q2, question 1 and 2; SJC, swollen joint count; SSZ, sulphasalazine; TJC, tender joint count; VAS, visual analogue scale.

Psoriasis

In psoriasis also, there are no randomised controlled trials available to compare T2T with routine treatment. The Modified Psoriasis Severity Score (MPSS) was used to titrate weekly dosage of methotrexate,³⁷ and the Psoriasis Area and Severity Index (PASI) was used to titrate ciclosporin³⁸ ³⁹ or mycophenolate mofetil³⁸ (table 1 and online supplementary table S2). Other than that, there has been no defined target to guide treatment escalation, although some studies used thresholds to decide whether to pause therapy—for example, to pause etanercept as soon as a target of PGA of ≤2 (clear, almost clear or mild) was reached.⁴⁰

DISCUSSION AND CONCLUSION

We present a systematic review of targeted treatment for SpA and psoriasis that informed the consensus-finding process of the expert committee for T2T-SpA recommendations.

Randomised trials designed to compare targeted treatment with another type of care are not available, but evidence can be derived from studies that apply target-oriented treatment adaptation. The majority of designs suggest use of the BASDAI to evaluate therapeutic response in AS (but other composite measures such as ASDAS⁴¹ ⁴² seem to be increasingly used), swollen and tender joint counts for PaA, and MPSS and PASI for psoriasis. In many studies, response was evaluated after 12–14 weeks,
while others stretched out to 36 weeks. Importantly, no information on long-term outcomes is available. Composite measures of disease activity have not yet been formally evaluated for PsA. Likewise, no such studies are available for other peripheral spondyloarthritides including reactive arthritis. Some trials for reactive arthritis used antibiotic therapy (reviewed by Hannu43). These studies are not included here because they did not use criteria for insufficient response.

The definition of pertinent treatment targets for SpA is challenging because of the heterogeneity of the disease, including axial, peripheral and extra-articular/extraspinal manifestations. Moreover, no data on a positive effect on physical function and radiographic damage resulting from a T2T strategy have been published for SpA.

The data presented informed the task force on the current state of evidence and clearly reveal that further research is needed. In particular, clinical trials comparing the value of treatment steered by levels of disease activity versus conventional therapy in SpA, both axial and peripheral, are needed.

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REFERENCES
Clinical and epidemiological research


7 http://www.abstracts2view.com/eular/[Online]


