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

M M Schoels,[1] J Braun,[2] M Dougados,[3] P Emery,[4] O Fitzgerald,[5] A Kavanaugh,[6] T K Kvien,[7] R Landewé,[8] T Luger,[9] P Mease,[10] I Olivieri,[11] J Reveille,[12] C Ritchlin,[13] M Rudwaleit,[14] J Sieper,[15] J S Smolen,[16] M de Wit,[17] D van der Heijde[18]

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For numbered affiliations see end of article.

Correspondence to
Dr Monika M Schoels, 2nd Department of Medicine, Centre for Rheumatic Diseases, Hietzing Hospital, Wolkersbergenstrasse 1, Vienna 1130, Austria; monika.schoels@live.com

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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] 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.[1]

However, no evidence that a guided treatment strategy is as effective for AS and PsA as it is for rheumatoid arthritis (RA)[3] 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.[4] 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,[5] 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 abstracts[7 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

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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, spondylodiscitis
- 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.

target versus a conventional, non-steered approach, as is available for RA.[10] Secondly, we reviewed ancillary literature providing circumstantial evidence that a steered therapy might be beneficial during long-term follow-up.

RESULTS

We initially retrieved 1976 publications in Medline and Embase, and 1002 in Cochrane. By title and abstract screening, we selected 159 of these for full-text review, and finally included 21 papers plus one additional publication found by hand-search. Of these, 12 trials enrolled patients with AS, five included patients with PsA, and two studies included both AS and PsA patients (table 1). No studies on peripheral SpA were obtained; three studies addressed patients with psoriasis. No conference abstracts and no trials from the NIH database provided data on treatment targets. Figure 1 illustrates the search and selection process.

The most important result of the search was the failure to find any randomised comparison evaluating a T2T approach versus routine treatment. However, several publications report on targets and timelines that were used as thresholds before escalating therapy.

Axial SpA (including AS and non-radiographic axial SpA)

Overall, we found 14 studies[11–24] with predetermined treatment targets in AS that were suitable for inclusion. Table 1 specifies the measures of disease activity or function and timelines as well as cut-off points used as indication of (in)sufficient response. The baseline characteristics of the study populations were comparable with regard to inclusion criteria, disease activity, function, age and disease duration (online supplementary table S2 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 weeks[18] 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 study[21] 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[18] 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 used combined targets, mostly combinations of the BASDAI[19 22] or the Bath AS Metrology Index (BASMI)[24] with either acute phase reactants[19 22] or the physician global assessment (PhysGA).[24] Meric *et al*[16] 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 therapy[13] and—expanded by the ESR—also to guide dose escalations of mesalazine.[20] Cheung *et al*[22] 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.[23 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,[21] BASDAI and serum IFX levels[16] (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 weeks[28] or ≥40% after 3 months.[29] Two trials[18 19] included mixed SpA populations and used ≥40% reduction in PGA after 14 weeks[18] or ESR and CRP[19] (table 1). Some prospective studies investigated the correlation between clinical symptoms and progression of radiographic damage and reported a predictive capacity of synovitis,[30–32] dactylitis[33] and CRP,[34] while other authors did not observe these associations.[35] 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.

Table 1 Treatment targets and timeline definition in trials of ankylosing spondylitis and psoriatic arthritis

Measure of disease activity	Target definition	Assessment after	Study (drug)
Ankylosing spondylitis			
ASAS	≥20% response	Week 12 (OLE)	ATLAS (ADA)*[11]
BASDAI	<3 at both current and prior assessment	Week 36	ASSERT (IFX)†[12]
ASAS	≥40% response	Week 12	Haibel (ADA)*[14]
BASDAI	≥50% reduction, or ≤3	Week 22 and 38	CANDLE (IFX)†[15]
BASDAI	≥20% reduction ≥50% reduction	Month 3 Month 6	Jois (IFX)[17]
BASDAI	≥40% reduction	Week 14	Cherouvim (IFX)*[18]
ESR	≥1 mm reduction per week: escalate ≤20 (women)/≤10 (men) mm/h for step down Remission: ESR ≤10 (men ≤5) and BASDAI, BASFI, BASG, BASMI scores mean <1: taper	Weekly for escalation Month 6 for step down	Darmawan (IS)†[21]
Combined/alternative targets			
Total back pain (VAS), MST (min)	≥20% reduction in both back pain and MST	Week 16	GO-RAISE (GOL)†[13]
BASDAI, IFX serum level	<40 and 5.0 μg/ml	After 4th IFX (~22 weeks)	Meric (IFX)*[16]
BASDAI, ESR/CRP	<4 (BASDAI) or <30 mm/h ESR and <5 mg/l CRP	Week 38	Collantes (IFX)†[19]
MST (VAS), pain (VAS), ESR	≥20% reduction in 2/3	Week 4	Van Denderen (mesalazine)*[20]
BASDAI, ESR/CRP	≥2 patients. BASDAI reduction and ≥20% ESR/CRP reduction	Week 2, then 6-weekly	Cheung (IFX)[22]
Q1: disease has remained under control? Q2: disease has been worsening? VAS pain, BASDAI	No relapse; definition: Q1 'Yes' and Q2 'No' and either <2/10 pain increase and <1/10 BASDAI increase	≥4 weeks after stopping for on-demand week 40 for dose escalation	Breban (IFX)†[23]
BASMI, PhysGA	No relapse; definition: ≤4 BASMI and ≤4 PhysGA	26 weeks after stop	Braun (IFX)†[24]
Psoriatic arthritis			
TJC and SJC	≥20% reduction	12 weeks	ADEPT (ADA)[25]
TJC and SJC	≥10% reduction	16 weeks	GO-REVEAL (GOL)[26]
TJC and SJC combined N	≥20% reduction	38 and 46 weeks	IMPACT 2 (IFX)[27]
Joint count 'actively inflamed'	≥30% reduction	14 weeks	Feletar (IFX)[28]
Joint count	≥40% reduction	3 months	Rahman (SSZ)[29]
PGA	≥40% reduction	14 weeks	Cherouvim (IFX)[18]
BASDAI, ESR/CRP	<4 (BASDAI) or <30 mm/h ESR and <5 mg/l CRP	Week 38 (cave diff AB 30/text38)	Collantes (IFX)†[19]
Psoriasis			
MPSS	$MPSS_{present\ visit} > MPSS_{previous\ visit} - 0.2 * (MPSS_{previous\ visit} - MPSS_{baseline})$	Max 18 weeks	De Jong (MTX)[37]
PASI	Improvement >25%	6 weeks	Beissert (CsA, MMF)[38]
PASI	Improvement ≥75%	12 weeks	Nevin (CsA)[39]

*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; CRP, C-reactive protein; CsA, ciclosporin; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; GOL, golimumab; IFX, infliximab; IS, immunosuppressant therapy (consisting of combined DMARDs); mesa, 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, sulfasalazine; 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 ciclosporin[38 39] or mycophenolate mofetil[38] (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 adaption. The majority of designs suggest use of the BASDAI to evaluate therapeutic response in AS (but other composite measures such as ASDAS[41 42] seem to be increasingly used), swollen and tender joint counts for PsA, and MPSS and PASI for psoriasis. In many studies, response was evaluated after 12–14 weeks,

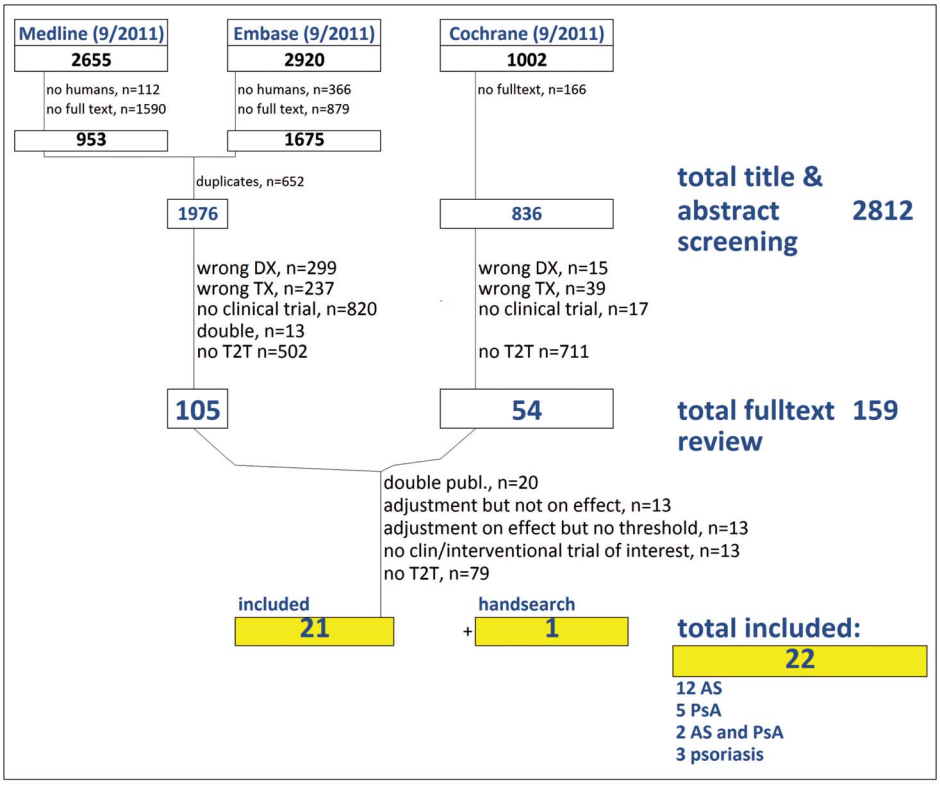

Figure 1 Search and selection process. AS, ankylosing spondylitis; clin, clinical; DX, diagnosis; PsA, psoriatic arthritis; publ., publication; T2T, treatment to target; TX, treatment.

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 Hannu[43]). 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.

Author affiliations
[1]2nd Department of Internal Medicine, Center for Rheumatic Diseases, Hietzing Hospital, Vienna, Austria
[2]Department of Rheumatology, Rheumazentrum Ruhrgebiet, Herne, Germany
[3]Department of Rheumatology, Hopital Cochin, Paris, France
[4]Section of Musculoskeletal Disease, University of Leeds, Leeds, UK
[5]Department of Rheumatology, St Vincents University Hospital, Dublin, Ireland
[6]University of California San Diego, La Jolla, California, USA
[7]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
[8]Department of Clinical immunology and Rheumatology, AMC Amsterdam, Amsterdam, The Netherlands
[9]Department of Dermatology, University of Münster, Münster, Germany
[10]University of Washington, Department of Rheumatology, Seattle, Washington, USA
[11]Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie, Potenza, Italy
[12]Department of Rheumatology, University Texas, Houston, Texas, USA
[13]Department of Rheumatology, University of Rochester Medical Center, Rochester, New York, USA
[14]Department of Medicine, Charité University Medicine, Berlin, Germany
[15]Medical Department I, Rheumatology, University Clinic Benjamin Franklin, Berlin, Germany
[16]Department of Rheumatology, Hietzing Hospital, Vienna, Austria
[17]Department of Medical Humanities, VU Medical Center, Amsterdam, The Netherlands
[18]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

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Supplementary Material on

Treating Spondyloarthropathies to Target –

A Systematic Literature Review Supporting Treatment Recommendations

including Supplementary Tables S1 (Search terms) and S2 (Studies, inclusion criteria at enrollment, patients baseline disease activity)

Table S1. Search terms

1	(treat$ adj4 target$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
2	(titrat$ or adjust$ or response-based).mp.
3	(optim$ or adapt$ or switch$ or add$ or chang$ or expand$ or step$ or combin$ or intensif$ or escalat$).ti.
4	((strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or control$) adj2 (treat$ or therap$)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
5	(lack$ and effic$).mp. or (insuffi$ and respon$).m_titl. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, sh, tn, dm, mf, dv, kw]
6	demand.m_titl. or demand.mp. or on-demand.mp.
7	((remission or ((low$ or moderate or medium or high) and activity)) adj3 (strateg$ or optimi$ or adapt$ or control$ or frequency or dose$ or dosing)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
8	*Disease Progression/ or *Disease Management/ or *Disease Outbreaks/ or Disease/ or ((strateg$ or proced$ or consequ$ or therap$ or halt$ or stop$ or revers$ or dela$ or arrest$ or detain$ or slow$ or preven$ or retard$ or avoid$) adj3 (structural or functional or erosi$ or progre$ or disabilit$ or invalidity or impediment or disablement or radiograph$ or radiolog$)).mp.
9	*Remission Induction/ or (strateg$ or aim$ or goal$ or target$ or tight$ or aggressiv$ or intens$ or control$).ti.
10	ankylosing spondylitis.mp. or ankylosing spondylitis/
11	psoriatic arthritis.mp. or psoriatic arthritis/
12	spondyl$.m_titl.
13	seronegative.m_titl.
14	(psoriasis or (skin and psoriatic and arthritis) or pasi).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
15	(randomized controlled trial or clinical trial).pt. or Double-Blind Method/ or "double blind:".mp. or Placebos/ or placebo:.mp. or random:.mp. or single-blind method/ or exp Clinical Trials/ or clinical trial$.mp. or ((singl$ or doubl$ or trebl$) adj2 (blind$ or mask$)).mp. or placebo$.mp. or exp Research Design/ or comparative study.pt. or exp Evaluation Studies/ or follow-up studies/ or prospective studies/ or (control$ or prospectiv$ or volunteer$).mp. or clinical trial.mp. or Clinical Trial/ or meta-analysis.mp. or Meta-Analysis/

Table S2. Studies and their inclusion criteria at enrollment, patient baseline disease activity

			BASELINE CHARACTERISTICS	
STUDY / AUTHOR; PY	INCLUSION CRITERIA		DISEASE ACTIVITY	FUNCTION
ANKYLOSING SPONDYLITIS	BASDAI	ADDITIONAL INCLUSION CRITERIA	BASDAI	BASFI
ATLAS 2006[1]	≥ 4	at least 2 of 3 clinical criteria: • BASDAI ≥ 4 • MST ≥ 1 hour • VAS total back pain ≥ 4 (0-10)	6.3±1.7	5.2±2.2
ASSERT 2005[2]	≥ 4	BASDAI ≥ 4 and VAS spinal pain ≥ 4 (0–10)	6.6 (5.3-7.6)	5.7 (4.5-7.1)
Inman 2008[3]	≥ 4	BASDAI ≥ 4 and VAS total back pain ≥ 4 (0–10)	6.8 (5.7-7.7)	5.2 (3.2-5.9)
Haibel 2008[4]	≥ 4	-	6.5±1.2	5.4±2.0
CANDLE 2010[5]	≥ 4	-	not stated	not stated
Meric 2010[6]	≥ 4	-	36.6 (0.0-73.9)	not stated
Jois 2006[7]	≥ 4	-	6.6 (4.2-8.7)#	6.4 (4.7-8.2)#
Cherouvim 2004[8]	≥ 3	BASDAI ≥ 3 and pain >3 months with VAS pain ≥ 4 on 2 successive occasions	not stated	not stated
Collantes-Estevez 2005[9]	not stated	-	not stated	not stated
Van Denderen 2003[10]	not applicable	at least one of four clinical crit. • MST>30min • Peripheral synovitis • Enthesopathy • VAS pain>2 plus one laboratory criteria: • ESR>20mm/h or • CRP>20mg/l	4.4±4.4	4.5±4.1
Darmawan 2006[11]			6.19±2.07	5.55±1.91
Cheung 2008[12]	not applicable	-	9.0 (8.3-9.6)* 8.5 (7.8-9.2)**p=n.sign.	7.0 (5.7-8.3)* 7.3 (6.2-8.5)**p=n.sign.
Breban 2008[13]	≥ 3	BASDAI ≥ 3 and VAS axial pain ≥ 3 and ≥ 1 of the following: • CRP more than twice ULN	6.2±1.5	5.4±2.0

			• positive MRT of spine or SI joints • enthesitis (power Doppler)		
Braun 2008[14]	≥ 4	BASDAI ≥ 4 and VAS spinal pain ≥ 4		6.4±1.4[15]	5.2±1.9[15]
PSORIATIC ARTHRITIS	**JOINT COUNTS**	**ADDITIONAL INCLUSION CRITERIA**		**SWOLLEN & TENDER JOINT COUNTS**	**HAQ**
Cherouvim 2004[8]	≥ 3 SJC and ≥ 3 TJC			not stated	not stated
Collantes-Estevez 2005[9]	not stated	not stated		not stated	not stated
ADEPT 2009[16]	≥ 3 SJC and ≥ 3 TJC[17]	-		SJC76: 14.3±12.2 TJC78:23.9±17.3[17]	1.0±0.6[17]
Kavanaugh 2009[18]	≥ 3 SJC and ≥ 3 TJC	SJC ≥ 3 and TJC ≥ 3 and negative RF	and at least 1 subset of PsA and plaque psoriasis with a lesion of ≥ 2cm Ø	SJC66: 12.0±8.4 TJC68: 22.5±5.7	not stated
IMPACT-2 2007[19]	≥ 5 SJC and ≥ 5 TJC	SJC ≥ 5 and TJC ≥ 5 and either • CRP≥ 15mg/l and/or • MST≥ 45 min	active psoriasis, with at least one plaque ≥ 2cm Ø	SJC66: 13.9±7.9 TJC68: 24.6±14.1	1.1±0.6
Feletar 2004[20]	≥ 6 SJC and / or ≥ 6 TJC	-		SJC66: 9.1±5.3	
Rahman 1998[21]	not stated	-		SJC: 15.4±9.1	
PSORIASIS	**INCLUSION CRITERIA**			**PASI**	**Others**
De Jong 2003[22]	Stable psoriasis for ≥ 3 months			not stated	MPSS=2.5[#]
Beissert 2009[23]	PASI ≥10			22.4±9.2 24.6±11.1	-
Nevin 1995[24]	not stated			21.7-54.2[$]	-

*Patients with spinal ankylosis; **patients without spinal ankylosis; Tender (TJC) and Swollen (SJC) are enlisted as specified in the respective manuscript. Where available, the applied number of joints (66 or 68 joint counts, etc) are specified. Mean±SD, median (Interquartilrange), #median (range), or $range are given; Ø=diameter; SI joints=sacroiliac joints; RF=rheumatoid factor; PASI=, MPSS=modified psoriasis severity score

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