International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (11-20), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Roles of Diagnosis and Management of Spondyloarthritis, Systematic Review

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Abstract: **The spondyloarthropathies (SpA) are a rheumatologic group of inflammatory diseases that include ankylosing spondylitis (AS), reactive arthritis (ReA), enteropathic spondylitis, or arthritis associated with inflammatory bowel disease (IBD), psoriatic arthritis (PsA), and undifferentiated spondyloarthropathy (uSpA). The aim of this systematic review was this to demonstrate and highlight the updates on the diagnosis and managment of spondyloarthritis throught evdiance based studies. Studies were retrieved by searching six electronic databases (MEDLINE/PubMed, EMBASE, PEDro, AMED, CINAHL, and The Cochrane Central Register of Controlled Trials) from their inception to October, 2016. Search terms were adapted for use with each database. Common keywords and medical subject headings were related to components: "spondyloarthritis," "ankylosing spondylitis," "sacroiliitis," "psoriasis arthritis," "reactive arthritis," "arthritis and inflammatory bowel disease," "inflammatory back pain, diagnosis and management." Based on several studies which were identified, NSAIDs are especially effective in patients with axial involvement, reducing pain and stiffness substantially in a majority of patients, as shown in a number of clinical trials with nonselective cyclooxygenase (COX) inhibitors as well as with selective COX-2 antagonists.**

Keywords: **spondyloarthropathies (SpA), ankylosing spondylitis (AS), reactive arthritis (ReA).**

1. INTRODUCTION

The spondyloarthropathies (SpA) are a rheumatologic group of inflammatory diseases that include ankylosing spondylitis (AS), reactive arthritis (ReA), enteropathic spondylitis, or arthritis associated with inflammatory bowel disease (IBD), psoriatic arthritis (PsA), and undifferentiated spondyloarthropathy (uSpA) [1].

The brand-new advancements in the clinical and medical elements of SpA were pursued by the requirement for brand-new methods for meaning of early medical diagnosis and result requirements for scientific research studies. The significant factor for this hold-up might be the low awareness of AS amongst the doctors as well as an absence of well specified requirements for recognizing clients with inflammatory back pain (IBP) from persistent low back pain of mechanical origin.

Depending upon the medical functions and imaging, SpA can be categorized as primarily peripheral or mainly axial [2,3] They are connected with reduced physical function, reduced work efficiency, and lower health-related lifestyle (QoL) [4,5,6] Raised cardiovascular threat aspects and increased cardiovascular morbidity and death have actually been connected with AS and PsA [7,8].

A methodical evaluation research study [9] which provided population occurrence for this condtion approximates for SpA, AS and PsA inning accordance with geographical locations. For USpA, rea and ibd-spa too couple of research studies were readily available to perform a metaanalysis and, for that reason, outcomes were just summed up. Occurrence price quotes of ReA (variety 0.0%-0.2%), IBD-SpA (variety 0.0%-0.1%), and uSpA (variety 0.0%-0.7%) were typically low [9].

The association with human leukocyte antigen (HLA)-B27, peripheral joint participation mainly of the lower extremities, sacroiliitis, spondylitis, enthesitis, dactylitis, uveitis, enteric mucosal sores and skin sores are the shared symptoms of the illness [10,11] Classification of a specific client into a subset of SpA can be challenging due to the absence of distinct requirements for the medical diagnosis [12] The recently established Assessment of SpondyloArthritis International Society (ASAS) category requirements proposes to categorize the SpA inning accordance with leading medical symptoms; primarily peripheral or mainly axial, with or without associated psoriasis, IBD or preceding infection [2,3].

The brand-new advancements in the clinical and medical elements of SpA were pursued by the requirement for brand-new techniques for meaning of early medical diagnosis and result requirements for medical research studies. There is a long hold-up, around 5-6 years, in between the very first incident of the SpA signs and the medical diagnosis of the illness specifically for woman, juvenile beginning or HLA-B27 unfavorable clients [13,14] The significant factor for this hold-up might be the low awareness of AS amongst the doctors along with an absence of well specified requirements for recognizing clients with inflammatory pain in the back (IBP) from persistent low pain in the back of mechanical origin. Reasonably late look of sacroiliitis on plain radiographs, due to perilous nature of AS, is another factor for hold-up. Current advancements showed that swelling of sacroiliac joints might be well envisioned by magnetic resonance imaging (MRI) long previously than radiographic modifications occur [15]

Spondyloarthropathies were officially categorized in Amor requirements in 1990. Amor's requirements are a list of indications based upon a scoring system of lab, scientific and radiologic functions and do not need an entry requirement [16] The check in the requirements contribute 1 point, 2 points or 3 points; a rating of 6 or more categorizes a client as having SpA. Sacroiliitis is not necessary for the medical diagnosis of SpA, it had the greatest rating (3 points) and is considered to be very specific for SpA (**Table 1**).

Table 1: Amor criteria for the classification of spondyloarthropathies [16]

Clinical symptoms or history of scoring	***Points***
Lumbar or dorsal pain at night or morning stiffness of lumbar or dorsal pain	1
Asymmetrical oligoarthritis	2
Buttock pain	1
If alternate buttock pain	2
Sausage like toe or digit	2
Heel pain or other well-defined enthesopathy	2
Iritis	1
Nongonococcal urethritis or cervicitis within 1 mo before the onset of arthritis	1
Acute diarrhea within one month before the 1 mo onset of arthritis	1
Psoriasis, balanitis, or inflammatory bowel disease (ulcerative colitis or Crohn's disease)	2
Radiological findings	
Sacroiliitis (bilateral grade 2 or unilateral grade 3)	3
Genetic background	
Presence of HLA-B27 and/or family history of ankylosing spondylitis, reactive arthritis, uveitis, psoriasis, or inflammatory bowel disease	

In this conducted systematic review we aimed to demonstrate and highlight the updates on the diagnosis and managment of spondyloarthritis throught evdiance based studies.

2. METHODOLOGY

Study design:

Systematic review was conducted

Search strategy:

Studies were retrieved by searching six electronic databases (MEDLINE/PubMed, EMBASE, PEDro, AMED, CINAHL, and The Cochrane Central Register of Controlled Trials) from their inception to October, 2016. Search terms were adapted for use with each database. Common keywords and medical subject headings were related to components: "spondyloarthritis," "ankylosing spondylitis," "sacroiliitis," "psoriasis arthritis," "reactive arthritis," "arthritis and inflammatory bowel disease," "inflammatory back pain, diagnosis and management." Different forms of spelling and synonyms for each term were also used.. No search restrictions were imposed. The electronic database search was supplemented by searching abstracts from the annual congresses of the World Confederation for this condition.

Different reviewers independently screened titles and abstracts to identify studies that potentially met the eligibility criteria. Full-texts of these reports were retrieved and assessed for eligibility by the same two reviewers. Foreign-language articles were translated into English.

3. RESULTS AND DISCUSSION

A. Diagnosis of spondyloarthritis:

We identified Twenty-five research studies that assessed the diagnostic energy of numerous imaging techniques in axSpA [17-41] 5 research studies reported on the diagnostic energy of radiography [17-21] They showed differing level of sensitivity (SE) and uniqueness (SP) of radiography in identifying sacroiliitis in inflammatory pain in the back (IBP)/ suspicion of SpA, while one observational research study reported an SE of 0.84 and an SP of 0.75 in identifying sacroiliitis in AS [17-21]. A single research study reported just reasonable arrangement in between radiography and CT in thought sacroiliitis and numerous incorrect favorable outcomes utilizing radiography [21]. 2 research studies reported greater SE for CT than radiography for identifying sacroiliitis (1 in AS, 1 in thought SpA) [18,20].

Thirteen research studies assessed the diagnostic energy of MRI showing differing SE and in general greater SP in clients with IBP or those with suspicion of SpA (**Table 2**) [22- 34] 3 research studies reported SE (0.73-0.9) and SP (0.9-0.97) for SI joint BME on MRI in recognized AS [25,26,28]. Wick et al [29] reported an SE of 0.11 and an SP of 0.93 for MRI SI joint disintegrations for medical diagnosis of AS, while Weber et al [28] reported that the combined functions of SI joint disintegration and/or BME increased SE to 0.98- 0.96 compared to BME alone (0.91- 0.83) without lowering SP and the location under the curve for medical diagnosis of AS. Heuft-Dorenborsch et al [30] discovered that preliminary evaluation of structural modifications by radiography followed by MRI evaluation of swelling with unfavorable radiography offers the greatest returns for finding participation of the SI joint in clients with current IBP [33]. 2 research studies discovered MRI of the SI joint remarkable to QSS or radiography for identifying sacroiliitis in IBP and SpA [17,36].

Table 2: summary of studies on the use of MRI in diagnosing axial spondyloarthritis

Studies	No.	Study population	Gold standard	SIJ/spine	MRI lesion	SE	SP	+LR	−LR
Longitudinal/RCT									
Bennett *et al*[22]	50	SpA	X-ray	SIJ	Grade 3 SI+HLAB27 27B27	0.62	0.92	7.7	0.41
Marzo-Ortega *et al*[23]	76	IBP (NSBP, HC)	Clinical diagnosis	SIJ	Grade 1 SI	0.82	0.43	1.4	0.41
					Grade 2 SI	0.73	1.0	∞	0.73
Oostveen *et al*[24]	25	IBP	X-ray	SIJ	Grade ≥2 SI	0.85	0.47	1.6	0.31
Cross-sectional/case-control									
Weber *et al*[25,26]	187	AS, IBP (NSBP, HC)	Clinical diagnosis	SIJ	BME (AS)	0.9	0.97	44.6	0.92
					BME (IBP)	0.51	0.97	26	0.50
					BME+ERO	0.81	0.97	27	0.19
Weber *et al*[27,28]	157	AS, IBP (NSBP, HC)	Clinical diagnosis	SIJ	BME	0.73	0.9	7.3	0.3
					BME and/or ERO	0.82	0.9	8.2	0.2
					FI	0.21	0.97	8.3	0.81
					FI with BME or ERO	0.24	0.97	9.2	0.78
Heuft-	68	IBP	X-ray	SIJ	chronic changes	0.49	0.97	16.3	0.52

Studies	No.	Study population	Gold standard	SIJ/spine	MRI lesion	SE	SP	+LR	−LR
Dorenbosch *et al*[30]									
Weber *et al*[33]	95	AS, IBP, (HC)	Clinical diagnosis	Spine	>2 CIL (AS)	0.69	0.94	12	0.32
					>2 CIL (IBP)	0.32	0.96	8	0.70
					LIL	0.97	0.31	1.4	0.09
Kim *et al*[34]	104	AS (HC)	Clinical diagnosis	Spine	MRI corner sign	0.44	0.96	11	0.58
Retrospective									
Wick *et al*[29]	179	AS (various)	Clinical diagnosis	SIJ	ERO	0.11	0.93	1.57	0.95
					BME	0.35	0.78	1.59	0.83
Bennett *et al*[31,32]	185	SpA (DA, IBP, HC)	Clinical diagnosis	SIJ and spine	>3 RLs	0.33	0.97	12.4	0.69
					Posterior BME lesion	0.13	0.99	14.5	0.87
					≥5 FRLs	0.22	0.98	12.6	0.79

- The terms of the individual original publications have been used in the table.

- AS, ankylosing spondylitis; BME, bone marrow oedema; CIL, corner inflammatory lesion; DA, degenerative arthropathy; ERO, erosion; FI, fatty infiltration; FRL, 'fatty Romanus' lesion; HC, healthy control; HLA27, human leucocyte antigen B27; IBP, inflammatory back pain; LIL, lateral segment inflammatory lesion; +LR, positive likelihood ratio; –LR, negative likelihood ratio; No., number of individuals included in the study; NSBP, non-specific back pain; RCT, randomised controlled trial; RL, 'Romanus' lesion; SE, sensitivity; SP, specificity; SI, sacroiliitis, SIJ, sacroiliac joints; SpA, spondyloarthritis.

Importance of early diagnosis in spondyloarthritides:

Ankylosing spondylitis (AS) in 90% or more cases, the illness begins with a sacroiliitis. It is crucial to tension that not all AS clients have or establish syndesmophytes. Even in clients with longer-standing illness, syndesmophytes are present in just about 50% of cases and just a smaller sized portion of these clients establish the common scientific image of clients with an ankylosed spinal column, where the name AS comes from. It is the most appropriate subtype for all clients with primarily spine signs and is related to together with PsA as the SpA with the most serious result. Its occurrence has actually been approximated to be in between 0.2% and 0.9% [11,42] and the illness typically begins in the 2nd years of life. The male-to-female ratio has actually been approximated more just recently to be around 2:1. In these clients, neck and back pain is the leading medical sign, which provides generally as inflammatory pain in the back that is defined by early morning tightness and enhancement by workout [43] In 90% or more cases, the illness begins with a sacroiliitis. Even more in the course of the illness, the entire spinal column can be impacted with spondylitis, spondylodisciitis, and arthritis of the little intervetebral joints [43] It is crucial to tension that not all AS clients have or establish syndesmophytes. Even in clients with longer-standing illness, syndesmophytes exist in just about 50% of cases and just a smaller sized portion of these clients establish the common medical image of clients with an ankylosed spinal column, where the name AS originates from. The term AS was presented around 1900 at a time when a medical diagnosis might be made just on the basis of the medical experience, without the assistance of imaging or lab outcomes. The term axial SpA, covering clients early in the course of the illness and clients with a less progressive course, appears to be more appropriate [44], whereas the term AS needs to be booked for the advanced 'ankylosed' stage of the illness.

B. Management of spondyloarthritis:

Inning accordance with the real evidence-based Assessment of Spondyloarthritis International Society (ASAS) and European League Against Rheumatism (EULAR) suggestions for the treatment of AS which was specified by Braun et al, [45] the model illness of axSpA, the first-line treatment of this illness include nonsteroidal anti-inflammatory drugs

(NSAIDs) and nonpharmacological treatment (such as education and routine exercise/physiotherapy) irrespectively of the of the primary participation (axial or peripheral) [45] (**Figure 1**)

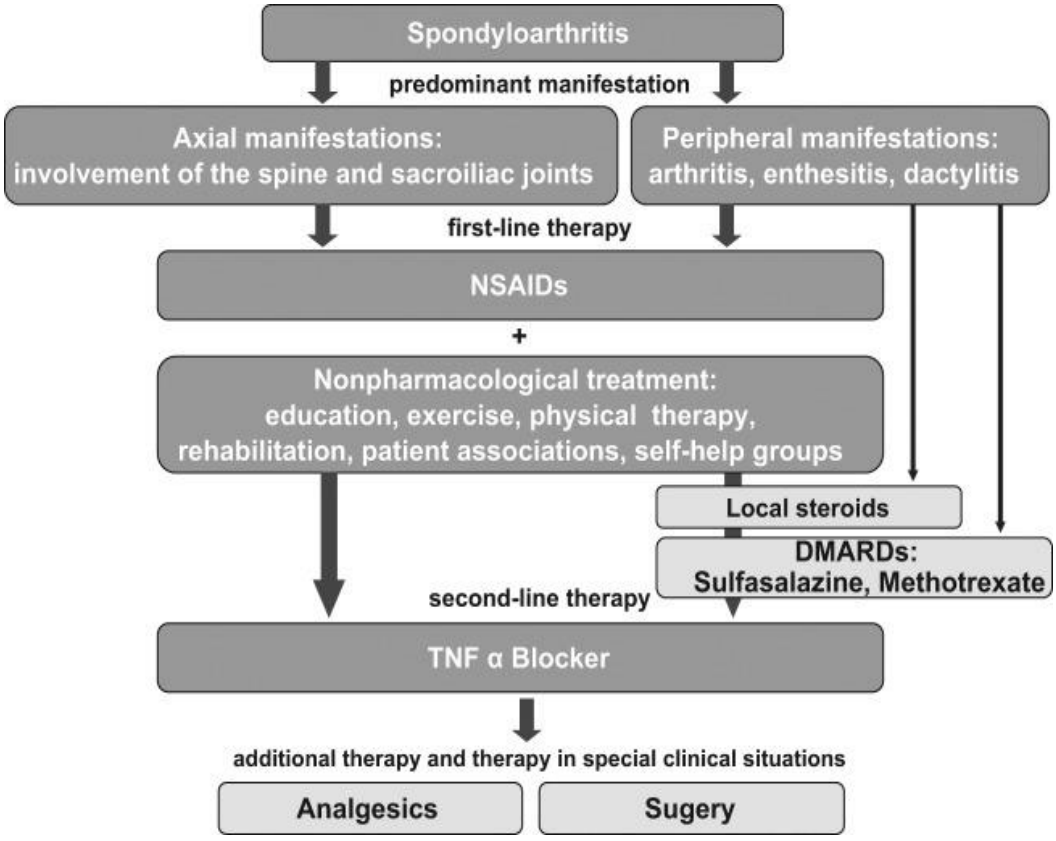

Figure 1: Summary of the ASAS/EULAR recommendations for treatment of AS. [45]

AS, ankylosing spondylitis; DMARD, disease-modifying antirheumatic drug; NSAIDs, nonsteroidal anti-inflammatory drug; TNF, tumour necrosis factor.

Based on several studies which were identified, NSAIDs are especially effective in patients with axial involvement, reducing pain and stiffness substantially in a majority of patients, as shown in a number of clinical trials with nonselective cyclooxygenase (COX) inhibitors as well as with selective COX-2 antagonists [46,47,48]. Clinically significant improvement of back pain in AS is usually reported by more than 60% of the patients treated with NSAIDs [47,48,49], as compared with only about 15% of patients with chronic low back pain of noninflammatory causes [49].

So far, clinical trials demonstrating clinical efficacy of NSAIDs in axSpA were performed in patients with AS only. However, it can be expected that NSAIDs are also effective in patients with nr-axSpA, who did not develop radiographic sacroiliitis yet. That is also being confirmed by daily practice. Considering nr-axSpA and AS as two stages of axSpA, it is reasonable to extrapolate data on treatment efficacy from AS to the early stage of the disease. Therefore, nr-axSpA patients should generally be treated in the same way as patients with AS [45].

Nonpharmacological treatment (first of all, education and regular exercises) is considered to be of nearly the same importance as NSAIDs in the first-line therapy of axSpA [45]. It is generally accepted that regular exercise/physiotherapy is effective in reducing symptoms and increasing function and spinal mobility in axSpA in a short-term perspective that is also supported by evidence [49]. However, the influence of nonpharmacological treatment on the long-term outcomes and radiographic spinal progression is less clear.

Classic disease-modifying antirheumatic drugs (DMARDs; such as methotrexate, sulfasalazine and, to a lesser extent, leflunomide) are usually not effective in axial disease, but might be beneficial in the case of peripheral joint involvement [51,52]. Therefore, DMARDs are currently reserved for patients with predominant peripheral manifestation.

Local steroids are also recommended mainly for treatment of peripheral manifestation (arthritis, enthesitis, dactylitis) but can be also effective in the treatment of active sacroiliitis (CT-guided injections) in pure axial disease [53].

In patients who do not respond to first-line therapy, a tumour necrosis factor (TNF) α blocker represents the only reliable treatment option available at the moment (**Figure 1**). Although, similarly to NSAIDs, the vast majority of evidence of TNF blockers efficacy in axSpA was obtained in clinical trials conducted in established AS, it is reasonable to expect the same (or even higher) clinical response in patients at the earlier disease stage, nr-axSpA. This idea was implemented in the recent update of the ASAS recommendation for treatment of axial SpA with anti-TNF α agents (**Figure 2**) [54]. According to these recommendations, patients with definite axSpA (fulfilling either the ASAS classification criteria for axial SpA [2]or the modified New York criteria for AS [55] having high disease activity (defined as Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥4) despite adequate NSAIDs treatment (defined as no response to at least two NSAIDs for at least 4 weeks in total unless contraindicated; local steroids and DMARDs might be used in patients with peripheral disease if appropriate) are considered as candidates for anti-TNF α therapy [56]. A positive opinion of a rheumatologist based on assessment of acute phase reactants, MRI, radiographic data and radiographic progression of AS is also required. Efficacy of anti-TNF α therapy should be assessed after at least 12 weeks of treatment and should first consider clinical improvement (BASDAI improvement by ≥50% or by ≥2 absolute points, 0–10 scale) [56].

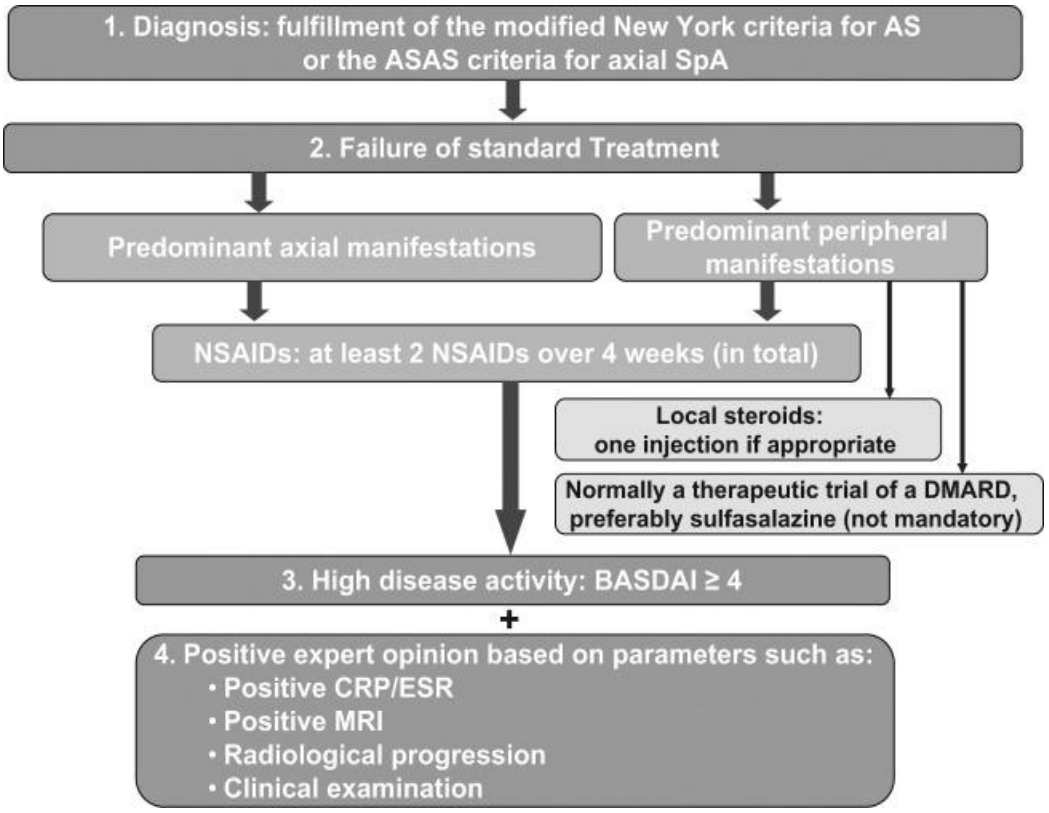

Figure2: ASAS recommendations for the use of an anti-TNF agent in patients with axial SpA [54].

Although the TNF-α inhibitors have proven to be effective in the treatment of SpA, there is a clinical need for new therapies with other mechanisms of action in these conditions; this need is due to the increasing number of nonresponder patients for whom TNF-α-inhibitor therapy is contraindicated. Among the newer therapies, targeting of IL-17, IL-12/23, and PDE4, seems to show more promising results than therapies targeting T-cell co-stimulation, B-cell surface antigens, and IL-6 (**Table 2**)

Table 2: pharmacological therapies for spondyloarthritis.

Drugs	Mechanism of action	Spa subtype(efficacy)	Extra-articular manifestation
Infliximab	Chimeric TNF inhibitor	AS[*‡], PsA[*‡], nr-axSpA	UC[*‡], CD[*‡], psoriasis[*‡], uveitis
Etanercept	Fusion protein TNF inhibitor	AS[*], PsA[*‡], nr-axSpA[*]	Psoriasis[*‡], uveitis?
Adalimumab	Fully human TNF inhibitor	AS[*‡], PsA[*‡], nr-axSpA[*]	UC[*‡], CD[*‡], psoriasis[*‡], uveitis
Golimumab	Fully human TNF inhibitor	AS[*‡], PsA	UC[*‡], uveitis
Certolizumab	PEGylated Fc-free TNF inhibitor	AS[*‡], PsA[*‡], nr-axSpA[*]	CD

Drugs	Mechanism of action	Spa subtype(efficacy)	Extra-articular manifestation
Abatacept	T-cell co-stimulation inhibitor	PsA?	
Rituximab	Anti-CD20 (anti-β cell)	AS?	
Tocilizumab	IL-6R inhibitor	PsA?	
Sarilumab	IL-6R inhibitor	?	
Secukinumab	IL-17A inhibitor	PsA, AS?	Psoriasis*
Ustekinumab	Fully human IL-12 and IL-23 inhibitor	PsA*‡	Psoriasis*‡
Apremilast	PDE4 inhibitor	AS, PsA*	Psoriasis*
Anakinra	IL-1 inhibitor	AS?, PSA?	

*Approved by the European Medicines Agency.

‡Approved by the US Food and Drug Administration.

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