

# Role of Agents other than Tumor Necrosis Factor Blockers in the Treatment of Psoriatic Arthritis

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**ABSTRACT.** Psoriatic arthritis (PsA) is a systemic inflammatory disease characterized by possible peripheral and axial joint involvement, enthesitis, dactylitis, and skin and nail disease. It affects up to one-third of psoriatic patients, and may be associated with comorbidities such as cardiovascular and metabolic diseases. The usually prescribed initial treatment of moderate-severe PsA is methotrexate, which may be accompanied or replaced by a tumor necrosis factor (TNF) inhibitor such as etanercept, infliximab, or adalimumab. However, some patients may become unresponsive (or have contraindications) to available anti-TNF agents and require alternative treatment. The aim of this review is to describe the potential role of some new immunomodulatory agents. (J Rheumatol Suppl. 2015 Nov;93:79–81; doi:10.3899/jrheum.150643)

## Key Indexing Terms:

PSORIATIC ARTHRITIS      TUMOR NECROSIS FACTOR INHIBITORS      APREMILAST  
USTEKINUMAB              INTERLEUKIN-17 INHIBITORS              RITUXIMAB

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy of unknown etiology<sup>1</sup> that affects as many as one-third of patients with psoriasis. It belongs to the rheumatic disease family of the spondyloarthritides (SpA), which also includes enteric-associated arthritis, reactive arthritis, ankylosing spondylitis (AS), and undifferentiated spondyloarthritis<sup>2</sup>, all of which are associated with arthritis of the axial skeleton, inflammatory back pain, uveitis, dermatological and gastroenterological involvement, and HLA-B27<sup>3</sup>. It affects both sexes equally (although men are 3 times more likely to show axial involvement), and usually appears at age 30 to 50 years. It has a number of manifestations, including mono-oligoarthritis, spondyloarthropathy with axial involvement, and enthesitis, and can be associated with complications such as metabolic and cardiovascular diseases<sup>4</sup>.

## THERAPY

Selecting the most appropriate treatment for PsA is not easy, but international guidelines have been published by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the European League Against Rheumatism (EULAR); and there are treatment

recommendations at the national level. The GRAPPA guidelines are based on 5 domains (peripheral arthritis, skin and nail involvement, enthesitis, dactylitis, and axial arthritis) and use a grid approach to account for various levels of disease activity and severity<sup>5</sup>, whereas the EULAR recommendations use algorithms mainly based on peripheral arthritis, and consider dactylitis, enthesitis, and skin and nail involvement separately<sup>6</sup>.

The aims of treating PsA are to alleviate the signs and symptoms of disease, inhibit structural damage, and maximize patients' quality of life. Nonsteroidal antiinflammatory drugs are often sufficient to treat mild PsA, and local intraarticular injections of corticosteroids may be used if only a few joints are involved. However, neither treatment has an effect on development of structural joint damage, and the findings of observational studies indicate that the same is true of disease-modifying antirheumatic drugs (DMARD), although there is a lack of randomized controlled trials (RCT) evaluating their real effect on PsA<sup>7,8</sup>.

## Anti-Tumor Necrosis Factor Drugs

Various studies have shown that patients with PsA have high TNF levels in synovial fluid and the synovium, and it has been found that anti-TNF agents (particularly etanercept, but also infliximab and adalimumab) are effective in reducing active joint inflammation and progression of radiographic damage; efficacious on skin manifestations, enthesitis, and dactylitis; and significantly improve function and quality of life<sup>9</sup>. It is also presumed that they are as effective on the spine in patients with PsA as they are in patients with AS.

However, some patients with severe PsA are (or become) resistant to anti-TNF agents or experience adverse events, and require alternative treatment (Table 1).

*Rituximab.* One study has revealed B cell lymphoid aggregates in PsA synovial tissue, and it has been reported that

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Table 1. Biological drugs approved for treating PsA.

Biological DMARD	Target	Structure
Etanercept	TNF- $\alpha$	Human TNF- $\alpha$ receptor p75Fc fusion protein
Infliximab	TNF- $\alpha$	Chimeric human-murine anti-TNF- $\alpha$ mAb
Adalimumab	TNF- $\alpha$	Recombinant human anti-TNF- $\alpha$ mAb
Certolizumab	TNF- $\alpha$	Fab' pegylated anti-TNF- $\alpha$
Golimumab	TNF- $\alpha$	mAb anti-TNF- $\alpha$
Ustekinumab	IL-12/IL-23	mAb that blocks p40

PsA: psoriatic arthritis; DMARD: disease-modifying antirheumatic drugs; TNF: tumor necrosis factor- $\alpha$ ; mAb: monoclonal antibody; IL: interleukin.

patients receiving rituximab (RTX) for non-Hodgkin lymphoma show the partial remission of psoriasis<sup>7,10</sup>. Cohen also described a case in which a patient with severe PsA treated with RTX experienced a dramatic clinical improvement and showed possible structural effects<sup>7a</sup>.

A number of small, open-label cohorts of patients with PsA have been administered the same RTX regimen as that used in rheumatoid arthritis (RA; two 1000-mg intravenous injections separated by 2 weeks), some of whom showed a slight improvement in joint count, although there was little effect on skin lesions. One possible off-label use of RTX is to treat patients with PsA and current or recent lymphoma in whom other agents are contraindicated. However, the need remains for clinical trials to demonstrate the effectiveness of RTX in patients with PsA or psoriasis.

**Tocilizumab.** Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody (mAb) that inhibits interleukin 6 (IL-6) signal transduction by preventing it from interacting with the membrane-expressed receptor and its soluble counterpart. It was approved in January 2009 in Europe (in 2010 in the United States) for treatment in adults with moderate and severe RA who cannot tolerate, or have failed to respond sufficiently to, DMARD or anti-TNF agents. It has been found that 24-week treatment with TCZ alone or in combination with methotrexate (MTX) is superior to MTX alone in reducing disease activity in patients with RA<sup>7,10,11</sup> and is also efficient in treating Castleman disease, adult-onset Still disease, Behçet diseases, Crohn disease, and juvenile inflammatory arthritis<sup>12,13</sup>.

Results of a pilot RCT on the use of IL-6 inhibitors in patients with PsA were disappointing. A published case study of 2 patients treated with TCZ for 6 months reported no improvement in arthritis or skin lesions, although both showed a reduction in serum C-reactive protein levels<sup>11,14</sup>. On the other hand, 2 cases have been published in which TCZ was effective in inducing resolution of articular manifestations<sup>15,16</sup>.

The tolerability of TCZ seems to be acceptable.

**Abatacept.** A phase II placebo-controlled study of the effect of different intravenous doses of abatacept (ABA) on PsA

found that 6-month treatment with a 10 mg/kg RA-labeled dose led to American College of Rheumatology 20% (ACR20) response in 48% of the patients. These clinical responses were corroborated by significantly improved magnetic resonance imaging scores, although the improvement in skin lesions was less marked. Nevertheless, the ACR and skin responses lasted 12 months in the completers, and those originally treated with placebo showed similar responses after being switched to ABA<sup>7</sup>.

**Ustekinumab.** Ustekinumab, which is approved for the treatment of adults with active PsA in the United States and Europe, is a fully human mAb that blocks the activity of p40, a protein subunit shared by IL-12 and IL-23, whose biological activity is consequently neutralized<sup>17</sup> (Table 1). It has also been shown to decrease the cutaneous mRNA expression of IL-12p40, IL-23p19, and interferon- $\gamma$  (INF- $\gamma$ ), inhibits IL-12- and IL-23-induced secretion of INF- $\gamma$ , IL-17A, TNF- $\alpha$ , IL-2, and IL-10, and is generally safe and well tolerated<sup>17</sup>.

Two large, well-designed trials found that it was significantly more effective than placebo in terms of ACR20 responses after 24 weeks, and the secondary endpoints of Psoriasis Area Severity Index (PASI) 75 response, enthesitis and dactylitis scores, radiographic progression, and Health Assessment Questionnaire-Disability Index scores. The responses were maintained for up to 100 weeks with and without concomitant MTX, and there were only rare serious infections or cardiovascular events<sup>17,18</sup>.

**IL-17 inhibitors.** IL-17 is an inflammatory cytokine secreted by Th17 T cells and other cells found in psoriatic plaques and inflamed entheses<sup>7,19</sup>. Three IL-17 inhibitors are currently undergoing advanced clinical testing: 2 IL-17A mAb (secukinumab and ixekizumab) and brodalumab, a mAb against IL-17 receptor A, all of which improve skin psoriasis.

A phase IIb RCT of secukinumab showed that 81% of the patients showed PASI 75 responses and 57% PASI improvement after 12-week treatment versus only 9% in the placebo group; and a randomized dose-finding study of ixekizumab showed significant PASI improvement in > 77% of treated patients and 8% in the placebo group<sup>7</sup>. Brodalumab has also been studied in PsA: subcutaneous doses of 140 mg and 280 mg, respectively, led to 12-week ACR20 responses in 36.8% and 39.3% of the patients, compared with 18.2% for placebo. However, further longer-term studies are necessary to define the effects of IL-17 inhibitors on the various manifestations of PsA<sup>7</sup>.

**Apremilast.** Apremilast is an oral inhibitor of phosphodiesterase 4, the main phosphodiesterase expressed in immune cells that degrades cyclic adenosine monophosphate (cAMP) into AMP<sup>7</sup>. This increases the intracellular levels of cAMP, which partially inhibits the expression of inflammatory cytokines IL-12, IL-23, TNF- $\alpha$ , and IFN- $\gamma$ , and increases the expression of antiinflammatory IL-10. The encouraging results and mild adverse reactions observed in phase II

clinical trials led to apremilast being used in phase III studies designed to evaluate further its effects on PsA, and preliminary results of the PALACE-1 study confirmed its clinical efficacy and safety<sup>20</sup>. It was therefore approved by the US Food and Drug Administration for use in adults with active PsA in March 2014, and it is currently being considered for registration in Canada and Europe.

Although pharmacological treatment often begins with MTX, anti-TNF therapies are still the gold standard for the treatment of PsA. However, as many patients become unresponsive to current treatments or develop side effects, it is important to continue seeking alternatives. Ustekinumab, which is approved for the treatment of adults with active PsA, represents one of these new opportunities.

## REFERENCES

1. Mease PJ. Psoriatic arthritis: update on pathophysiology, assessment and management. *Ann Rheum Dis* 2011;70 Suppl 1:i77-84.
2. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.
3. Chandran V, Raychaudhuri SP. Geoeconomics and environmental factors of psoriasis and psoriatic arthritis. *J Autoimmun* 2010;34:314-21.
4. Costa L, Caso F, D'Elia L, Attenu M, Peluso R, Del Puente A, et al. Psoriatic arthritis is associated with increased arterial stiffness in the absence of known cardiovascular risk factors: a case control study. *Clin Rheumatol* 2012;31:711-5.
5. Ritchlin CT, Kavanaugh A, Gladman DD, Mease PJ, Helliwell P, Boehncke WH, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis* 2009;68:1387-94.
6. Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, et al. European League Against Rheumatism. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis* 2012;71:4-12.
7. Mease PJ. Psoriatic arthritis treatment update. *Bull NYU Hosp Jt Dis* 2012;70:167-71.
- 7a. Cohen JD. Successful treatment of psoriatic arthritis with rituximab. *Ann Rheum Dis* 2008;67:1647-8.
8. Kingsley GH, Kowalczyk A, Taylor H, Ibrahim F, Packham JC, McHugh NJ, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology* 2012;51:1368-77.
9. Atzeni F, Sarzi-Puttini P, Vena G. Resistant cases of psoriatic arthritis: how to manage them. *J Rheumatol Suppl.* 2009 Aug;83:73-5.
10. Tak PP, Kalden JR. Advances in rheumatology: new targeted therapeutics. *Arthritis Res Ther* 2011;13 Suppl 1:S5.
11. Atzeni F, Ventura D, Batticciotto A, Boccassini L, Sarzi-Puttini P. Interleukin 6 blockade: tocilizumab in psoriatic arthritis. *J Rheumatol Suppl.* 2012 Jul;89:97-9.
12. Elkayam O, Jiries N, Dranitzki Z, Kivity S, Lidar M, Levy O, et al. Tocilizumab in adult-onset Still's disease: the Israeli experience. *J Rheumatol* 2014;41:244-7.
13. Caso F, Iaccarino L, Bettio S, Ometto F, Costa L, Punzi L, et al. Refractory pemphigus foliaceus and Behçet's disease successfully treated with tocilizumab. *Immunol Res* 2013;56:390-7.
14. Ogata A, Umegaki N, Katayama I, Kumanogoh A, Tanaka T. Psoriatic arthritis in two patients with an inadequate response to treatment with tocilizumab. *Joint Bone Spine* 2012;79:85-7.
15. Hughes M, Chinoy H. Successful use of tocilizumab in a patient with psoriatic arthritis. *Rheumatology* 2013;52:1728-9.
16. Costa L, Caso F, Cantarini L, Del Puente A, Scarpa R, Attenu M. Efficacy of tocilizumab in a patient with refractory psoriatic arthritis. *Clin Rheumatol* 2014;33:1355-7.
17. McKeage K. Ustekinumab: a review of its use in psoriatic arthritis. *Drugs* 2014;74:1029-39.
18. Weitz JE, Ritchlin CT. Ustekinumab: targeting the IL-17 pathway to improve outcomes in psoriatic arthritis. *Expert Opin Biol Ther* 2014;14:515-26.
19. Fiocco U, Accordi B, Martini V, Oliviero F, Facco M, Cabrelle A, et al. JAK/STAT/PKCδ molecular pathways in synovial fluid T lymphocytes reflect the in vivo T helper-17 expansion in psoriatic arthritis. *Immunol Res* 2014;58:61-9.
20. Mazur M, Karczewski J, Lodyga M, Zaba R, Adamski Z. Inhibitors of phosphodiesterase 4 (PDE 4): A new therapeutic option in the treatment of psoriasis vulgaris and psoriatic arthritis. *J Dermatolog Treat* 2014 Dec 29 (E-pub ahead of print).