

# New Biological Treatments for Psoriatic Arthritis

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**P**soriatic arthritis (PsA) is a chronic inflammatory arthropathy of unknown etiology [1] that affects as many as one-third of patients with psoriasis. Together with entero-associated arthritis (EA), reactive arthritis (ReA), ankylosing spondylitis (AS) and undifferentiated spondyloarthritis (uSpA), it is a member of the spondyloarthritis (SpA) family of rheumatic diseases [2] whose overlapping features include arthritis of the axial skeleton, inflammatory back pain, uveitis, dermatological and gastroenterological involvement, and a genetic association with human leukocyte antigen (HLA)-B27. It affects men and women equally (although the presence of axial disease is three times more frequent in men), and appears mainly between the ages of 30 and 50 years. Its various manifestations include mono-oligoarthritis, an erosive and destructive polyarthritis that cannot be distinguished from rheumatoid arthritis, and spondyloarthropathy with axial involvement or enthesitis, but it is also complicated by comorbidities such as cardiovascular and metabolic diseases.

## ETIOPATHOGENESIS

The etiopathogenesis of PsA is still unclear but involves both genetic and environmental factors. Pro-inflammatory cytokines are major mediators of systemic and local inflammation, and high interleukin 1 (IL-1), IL-6 and tumor necrosis factor (TNF) levels have been observed in psoriatic skin lesions and the synovial tissue of patients with rheumatoid arthritis (RA) or PsA [3]. The synovial infiltrate associated with both diseases has a similar number of fibroblast-like synoviocytes, but the synovium of PsA patients is characterized by a less hyperplastic lining and fewer monocytes/macrophages [3].

Although there are also considerably fewer T cells, T cells are probably involved in the pathogenesis of both psoriasis and PsA because a subset of specific T cells may be sufficient to promote inflammation and regulatory T cells may have anti-inflammatory effects. A recent study of abatacept (a selective

inhibitor of T cell activation as a result of its competitive binding to CD80 or CD86) has shown that it is efficacious for joints but has less effect on skin lesions [6]. It is also known that T-helper (Th) cells producing IL-17 (Th17 cells, which also produce TNF, IL-21 and IL-22) play a role in chronic inflammatory conditions and are stimulated by IL-23, which is highly expressed in psoriatic plaques [3]. The role of IL-23 in PsA is not clear, but the Th17-related cytokines IL-17 and IL-23 are expressed in the joints of PsA and RA patients, and ongoing clinical studies of the Th17 axis are investigating whether it can be used in the treatment of PsA.

The expression of TNF $\alpha$ , IL-1 $\beta$ , IL-6 and IL-18 is equally high in patients with PsA and in those with psoriasis, and published data support the view that blocking TNF $\alpha$  together with IL-1 $\beta$ , IL-6, IL-18 and IL-23 may be effective in PsA.

## TREATMENT

Due to the clinical heterogeneity of PsA, selecting the most appropriate treatment is a challenge. Some countries have published treatment recommendations, as have international groups such as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the European League Against Rheumatism (EULAR). The GRAPPA recommendations consider five domains (peripheral arthritis, skin and nail involvement, enthesitis, dactylitis, axial arthritis) and use a grid approach to account for various levels of disease activity and severity [4]. The EULAR recommendations use an algorithmic approach that mainly considers peripheral arthritis, with dactylitis, enthesitis and skin and nail involvement being considered separately [5].

The aims when initiating PsA treatment are to alleviate signs and symptoms, inhibit structural damage, and maximize the patient's quality of life. Mild PsA is often successfully treated with non-steroidal anti-inflammatory drugs (NSAIDs), although local intra-articular injections of corticosteroids may be used if only a few joints are involved. Neither, however, inhibit the development of structural joint damage.

PsA treatments have often been borrowed from RA, but there is a lack of randomized and controlled trials (RCTs) evaluating the impact of disease-modifying anti-rheumatic drugs (DMARDs) on PsA [6], although the findings of observational studies indicate that traditional DMARD therapy has little control over structural damage.

#### • DMARDS

One observational cohort study of 23 patients treated with methotrexate (MTX) for 2 years found no reduction in radiological progression in comparison with matched controls [7], although other authors have found that the early administration of high dose MTX significantly decreases actively inflamed joint counts and psoriasis and somewhat reduces radiological progression. An open-label study comparing MTX with MTX+infliximab in patients with early disease observed not only very good joint and skin responses in the patients receiving the combination, but also substantial improvements in those receiving MTX alone, which is in line with everyday clinical experience. Leflunomide is effective, and was formally approved for the treatment of PsA in Europe. Cyclosporin can rapidly ameliorate psoriatic skin lesions, but there is little evidence that it is effective in musculoskeletal disease, and its use is limited by the adverse effects of hypertension and renal insufficiency. However, it has been used in combination with anti-TNF agents such as etanercept [8].

#### • ANTI-TNF DRUGS

A number of studies have shown that PsA patients have high TNF levels in synovial fluid and the synovium, and it has been demonstrated that all anti-TNF agents slow radiographic progression and improve the patient's quality of life [8].

TNF inhibitors are effective in joints, skin, enthesitis and dactylitis in PsA patients, inhibit structural damage, and significantly improve function and quality of life [8], and it is presumed that they are as effective in the spine as they are in patients with AS. Furthermore, RCTs involving PsA patients have shown that they are also effective in reducing active joint inflammation and radiographic damage [8]. However, some patients with severe PsA are resistant to anti-TNF agents or develop adverse events and require alternative treatment.

#### • RITUXIMAB

One recent study has shown the presence of B cell lymphoid aggregates in PsA synovial tissue, and the partial remission of psoriasis has been reported in patients receiving rituximab for non-Hodgkin lymphoma [6,9]. Furthermore, Cohen has described a case in which rituximab led to a dramatic clinical improvement and possible structural effect in a patient with severe PsA [6].

A number of small open-label cohorts of PsA patients have received rituximab administered with the same regimen as that used in RA (two intravenous injections of 1000 mg separated by an interval of 2 weeks), some of whom showed a slight improvement in joint counts although there was little impact on skin lesions. One logical off-label application of rituximab would be to treat a patient with PsA and current or recent lymphoma in whom other agents are contraindicated. However,

the possible use of rituximab to treat PsA and psoriasis still needs to be confirmed by clinical trials.

#### • TOCILIZUMAB

Tocilizumab is a recombinant humanized monoclonal antibody (mAb) that inhibits the signal transduction of IL-6 by preventing it from interacting with both the membrane-expressed receptor and its soluble counterpart. It has been approved for the treatment of moderate and severe RA in adults who have inadequately responded to or been intolerant of previous DMARD or anti-TNF therapy (in Europe in January 2009 and the United States in 2010). Treatment with tocilizumab alone or in combination with MTX for 24 weeks is superior to MTX alone in reducing disease activity in RA patients [6,9,10], and has also been reported to be efficient in treating Castleman's disease, adult-onset Still's disease, Crohn's disease and juvenile inflammatory arthritis.

However, a pilot study (RCT) of the effects of IL-6 inhibitors on PsA did not lead to good results, and a recent case study of two patients treated with tocilizumab for 6 months did not ameliorate arthritis or the skin lesions, although it did lead to a decrease in serum C-reactive protein (CRP) in both patients [10]. The tolerability of tocilizumab seems to be acceptable.

#### • ABATACEPT

A phase II placebo-controlled study of the effect of various intravenous doses of abatacept on PsA found that 6 months treatment with the RA-labelled dose of 10 mg/kg led to ACR 20 responses in 48% of the patients. The clinical response data were corroborated by a significant improvement in magnetic resonance imaging (MRI) scores, although the improvement in the skin lesions was less marked. Nevertheless, the ACR and skin responses were maintained in the abatacept-treated group after 12 months, and the patients originally receiving placebo showed similar responses [6].

#### • USTEKINUMAB

Ustekinumab is a fully human mAb that has been approved for the treatment of psoriasis and PsA. It blocks the activity of p40, a protein subunit shared by IL-12 and IL-23, thus neutralizing their biological activity. It has been shown that it decreases the mRNA expression of IL-12p40, IL-23p19 and interferon-gamma (INF $\gamma$ ) in the skin, inhibits IL-12 and IL-23-induced INF $\gamma$ , IL-17A, TNF $\alpha$ , IL-2 and IL-10 secretion, and is generally safe and well tolerated.

#### • IL-17 INHIBITORS

IL-17, an inflammatory cytokine secreted by Th17 T cells and other cells, has been identified in psoriatic plaques and inflamed entheses [6]. Three IL-17 inhibitors are currently being tested in advanced-phase clinical trials: secukinumab and ixekizumab are mAbs against IL-17A, and brodalumab

is a mAb against IL-17 receptor A (IL-17RA). They have all been shown to improve skin psoriasis: a phase IIb RCT of secukinumab found a psoriasis area severity index (PASI) of 75 and PASI improvements in respectively 81% and 57% of the patients after 12 weeks, compared with 9% for placebo; and a randomized dose-finding study of ixekizumab showed significant PASI improvements in > 77% of patients compared with 8% for placebo [6]. Brodalumab has also been studied in PsA: subcutaneous doses of 140 mg and 280 mg respectively led to 12 week ACR 20 responses (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 [6].

#### • APREMILAST

Apremilast is an oral phosphodiesterase-4 inhibitor that regulates inflammatory mediators. Phosphodiesterase-4, the dominant phosphodiesterase expressed in immune cells, degrades cyclic AMP (cAMP) into AMP [6]. Thus, its inhibition increases intracellular cAMP levels, which can down-regulate inflammatory responses by partially inhibiting the expression of the inflammatory cytokines IL-12, IL-23, TNF $\alpha$  and IFN $\gamma$ , and increasing the expression of the anti-inflammatory mediator IL-10. Apremilast has been used in several studies of PsA patients and was shown to be efficacious and well tolerated, with minimal effects on any laboratory parameters.

#### CONCLUSIONS

Although pharmacological treatment often begins with MTX, anti-TNF therapies remain the gold standard. However, since

many patients become refractory to current treatment options or develop side effects, it is important to find new and effective drugs for the treatment of PsA.

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