New approved drugs for psoriatic arthritis

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SUMMARY

Psoriatic arthritis (PsA) is a chronic inflammatory disease that possibly leads to structural damage and to a reduction of joint function and poor quality of life. Treatment of PsA has changed since its introduction of anti-TNF drugs, which have shown to reduce the symptoms and signs of the disease and slow the radiographic progression. However, recently, the discovery of new pathogenic mechanisms have made possible the development of new molecules that target pro-inflammatory cytokines involved in skin, joint and entheseal inflammation. New drugs like ustekinumab, secukinumab and apremilast inhibit interleukin axis and intracellular pathways and showed their efficacy and safety in randomized clinical trials. These drugs have been recently approved for the treatment of PsA and included in the new EULAR and GRAPPA treatment recommendations. The aim of this paper is to briefly review the clinical trials that led to their approval for PsA.

Key words: *Psoriatic arthritis; treatment; ustekinumab; secukinumab; apremilast.*

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by the association of musculoskeletal involvement and psoriasis with a variable clinical course (1) and potentially associated to functional disability and poor quality of life (1, 2). The introduction of tumor necrosis factor (TNF) inhibitors dramatically changed the outcome of PsA patients.

Data coming from over ten years of experiences with randomized clinical trials and observational studies showed the efficacy of anti-TNF in all PsA domains (peripheral arthritis, axial involvement, enthesitis, dactylitis and extra-articular manifestations) and in reduction of radiographic progression (3, 4).

These agents proved to have significantly better responses than placebo, with American College of Rheumatology (ACR) 20 improvement criteria of 51-59% for TNF inhibitors *vs* 9-24.3% for placebo over 12-24 weeks of treatment (5). Clinical and laboratory indices showed similar favorable outcomes for all of anti-TNF drugs: in two indirect comparison meta-analyses, adalimumab, etanercept, golimumab, and infliximab, showed no important differences in the effectiveness and safety (6, 7). In this scenario, despite improved therapeutic benefits with TNF inhibitors, an unmet need remains the disease control in patients who are non-responders. In recent years, the understanding of the immunologic processes in the pathogenesis of disease led to the development of new terapies for PsA, based on the discovered cell pathways and cytokines involved. T-helper (Th) cells producing interleukin (IL)-17 (Th17 cells), seem to play a pivotal role in chronic inflammatory conditions and are stimulated by IL-23, which is highly expressed in psoriatic plaques, synovium and enthesis. Furthermore, other molecules such as phosphodiesterase (PDE) 4, seem to have a relevant role in the activation of immune cells and in the cytokines production. Blocking these cytokines and cellular pathways is now possible using biotechnological drugs and small molecules that were recently approved for the treatment of PsA. The aim of this paper is to briefly review the new drugs for the treatment of PsA.

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BLOCKING INTERLUKIN-12/23 AND INTERLUKIN-17 AXIS: USTEKINUMAB AND SECUKINUMAB

IL-12 is a heterodimer formed by a 35-kDa light chain (p35) and a 40-kDa heavy chain (p40). The two-receptor chains for IL-12 (12Rβ1 and IL-12Rβ2) are expressed mainly by activated T cells and natural killer cells but also on other cell types, such as dendritic cells (DCs) and B-cell lines. Similar to other pro-inflammatory cytokines, the production of IL-12 is regulated by different exogenous and endogenous stimuli: bacteria and material from microorganisms (including intracellular parasites, fungi, double-stranded RNA, bacterial DNA and CpG-containing oligonucleotides) are inducers of IL-12 production by macrophages, monocytes, neutrophils and DCs. These products engage Toll like receptor on phagocytes and DCs and thus lead to IL-12 production. IL-12 seems to play an important role in host innate response to bacteria, viruses and fungi and is responsible for the activation of Th1 response (8). The p40 heavy chain associates not only with IL-12 p35 to form IL-12, but also with another molecule, p19, to form the heterodimeric cytokine IL-23 (9). IL-23 binds to a receptor that is formed by IL-12Rβ1 and a new second chain, IL-23R. IL-12 and IL-23 play an important role in the pathogenesis of psoriasis and PsA: mutations in both IL-23 receptor and *IL-12* gene were associated with the susceptibility to psoriasis, inflammatory bowel disease and PsA, (10, 11) and, furthermore, IL-12 and IL-23 are essential for the induction and maintenance of the Th1/Th17 immune response, that are the two major phenotypes present in PsA and psoriasis (12). IL-23 activates Th17, which produces IL-17, a potent pro-inflammatory cytokine, activating DCs to produce IL-12, hence stimulating Th1. Moreover, IL-23 is essential for the proliferation and terminal differentiation of CD4+ Th17 T cells, maintaining IL-17 production, and ultimately driving the pathogenicity of these cells in multiple autoimmune models (12, 13). Recently, it has been shown that IL-23 is essential in enthesitis and acts on previously unidentified IL-23 receptor (IL-23R)+, on entheseal resident T cells, stimulating IL-17 expression and leading to specific IL-23 dependent inflammation in an animal model (14). IL-17 family includes six members (IL-17A-F) and there are several studies suggesting a role for IL-17A signaling in the pathogenesis of PsA. Polymorphisms associated with susceptibility to PsA are present in genetic loci involved in IL-17 signaling, such as IL-12B and TRAF3IP2. Levels of IL-17 receptor A (IL-17RA) and IL-17-positive T cells are elevated in synovial fluid and psoriatic plaques of patients with PsA. Of note, patients with spondyloarthritis, including PsA and ankylosing spondylitis, show higher levels of circulating Th17 cells in respect to rheumatoid arthritis patients (15). IL-17 has also been involved in both inflammation and bone remodeling in a murine model of spondyloarthritis: abundant in synovial fluids, IL-17 stimulated osteoclastogenesis in an osteoblast-dependent manner. Furthermore, IL-17 stimulated bone resorption in combination with TNF in fetal mouse long bones and induced the expression of the receptor activator of nuclear factor kappa-B ligand (the osteoclast differentiation factor) in osteoclast-supporting cells (16). In humans, IL-17 and TNF seem to be the two major cytokines involved in the structural damage of affected joints. On this basis, the inhibition of IL-12/23 and IL-17 axis proved to be effective in several autoimmune diseases, such as rheumatoid arthritis, psoriasis, multiple sclerosis and spondyloarthritis.

Ustekinumab

Ustekinumab is a fully human IgG1κ monoclonal antibody that binds to the common p40 subunit shared by IL-12 and IL-23, and it is the first non anti-TNF biologic approved for the treatment of PsA. Ustekinumab therapy rapidly decreased expression of a variety of pro-inflammatory cytokine codifying genes in psoriatic skin lesions including *p19*, *p40*, and *IL-17A* (17, 18). Ustekinumab demonstrated efficacy in the treatment of chronic plaque

psoriasis. Furthermore, ustekinumab 45 or 90 mg was superior to etanercept over a 12-week period in patients with psoriasis (19). In PsA, two-phase 3 studies (PSUMMIT 1 and 2) reported the efficacy and safety of ustekinumab in the treatment of all manifestations of the disease. In PSUMMIT 1, 615 naïve to anti-TNFα patients with active PsA were randomly assigned to placebo, 45 mg ustekinumab, and 90 mg ustekinumab. At week 24, a significantly higher proportion of patients in the ustekinumab groups than in the placebo group achieved an ACR20, ACR50 and ACR70 response (42.4, 24.9 and 12.2% respectively for ustekinumab 45 mg). Furthermore both ustekinumab dosages showed efficacy in improving quality of life [reduction of both health assessment questionnaire disability index (HAQ) and short form-36] in respect to placebo (20). In PSUMMIT 2 trial, patients with PsA previously exposed to TNF inhibitor were also enrolled. In this study more ustekinumab-treated patients (43.8% combined) than placebo-treated patients (20.2%) achieved ACR20 at week 24. ACR50 (P<0.05), HAQ improvement (P<0.001), and psoriasis area and severity index (PASI) 75 (P<0.01) also showed statistically significant differences. The extension study through week 52 showed that all benefits from ustekinumab were maintained. Of note, clinical responses tended to be lower among patients previously exposed to anti-TNF compared with anti-TNF-naïve patients (21). The numbers of patients with adverse events (including serious adverse events) and the types of events were similar across treatment groups in both studies and no deaths, opportunistic infections, cases of tuberculosis, or malignancies were reported (21). Ustekinumab treatment was generally safe and well tolerated in the two randomized studies with low number of injection site reactions. Recently, the analysis of the largest registry of ustekinumab-treated patients [the 2014 psoriasis longitudinal assessment and registry (PSOLAR)] on over 12,000 psoriasis patients identified no increased risk of malignancy, major adverse cardiovascular events, serious infection, or mortality (22). Ustekinumab significantly inhibits radiographic progression and joint damage in patients with active PsA: data coming from PSUMMIT 1 and 2 showed that, at week 24, significantly higher proportions of ustekinumab-treated (91.7%) than placebo-treated (83.8%; P=0.005) patients demonstrated no radiographic progression, as defined by change in total PsA-modified van der Heijde score from baseline (23). Clinical and radiographic benefits from ustekinumab treatment were maintained throughout 2 years of observation in patients enrolled in PSUMMIT 1 (24). Furthermore, ustekinumab treatment shows efficacy in all PsA clinical features. In PSUMMIT 1 there was a significant reduction in the number of patients with active enthesitis and dactylitis in respect to placebo and data also show a bath ankylosing spondylitis disease activity index 20, 50 e 70% result significantely higher in reducing the disease activity of patients with axial involvement (21).

Secukinumab

Secukinumab is a fully human IgG1κ monoclonal antibody that selectively binds to IL-17A cytokine and inhibits its interaction with the IL-17 receptor. Anti-IL-17A drug secukinumab showed to be superior to ustekinumab (CLEAR study) (25) and etanercept (FIXTURE study) (26) by PASI 90 and 75 response in patients with psoriasis, with a similar rate of adverse events. Anti-IL-17A drug secukinumab was also tested in two-phase 3, double-blind, placebo-controlled studies. In the FUTURE 2 study, adults (aged ≥18 years old) with active PsA were randomly allocated in a 1:1:1:1 ratio to receive subcutaneous placebo or secukinumab 300, 150, or 75 mg once a week from baseline and then every 4 weeks from week 4. A significantly higher proportion of patients achieved an ACR20 at week 24 with secukinumab 300 mg [54% of patients; odds ratio *vs* placebo 6.81, 95% confidence interval (CI)=3.42-13.56; P<0.0001], 150 mg (51% of patients; 6.52, 95% CI=3.25-13.08; P<0.0001), and 75 mg (29% of patients; 2.32, 95% CI=1.14-4.73; P=0.0399) *vs* placebo (15% of patients).

ACR50 was reached by 35% of patients in both secukinumab 300 and 150 mg groups and in 18% of patients in secukinumab 75 mg group at week 24. Up to week 16, the most common adverse events were upper respiratory tract infections (4, 8, 10 and 7% with secukinumab 300, 150, 75 mg, and placebo, respectively) and nasopharyngitis (6, 4, 6 and 8%, respectively). Serious adverse events were reported by 5, 1, and 4% of patients in the secukinumab 300, 150, and 75 mg groups, respectively, compared with 2% in the placebo group. No deaths were reported (27). In the FUTURE 2 study, responses in anti-TNF naive and anti-TNF treated subjects were sustained through week 52, with an ACR20 response rate of 68.7 and 54.5% respectively (28). Moreover, resolution of enthesitis and dactylitis was found in 69.2 and 65.9% of patients at week 52. The authors reported that subcutaneous secukinumab 300 and 150 mg improved the signs and symptoms of PsA, suggesting that secukinumab is a potential future treatment option for patients with this disease (27). Furthermore secukinumab significantly inhibits radiographic progression in peripheral joints in respect to placebo at week 24. Sustained inhibition of radiographic progression was observed through week 52 (29). FUTURE 1 study confirmed the efficacy of secukinumab, however some concern remains about the risk of infections and cardiovascular diseases and long term studies are needed (30).

INHIBITION OF PHOSPHODIESTERASE 4

PDEs are the enzymes that hydrolyze and degrade cyclic adenosine monophosphate (cAMP) (31). PDE4 is a cAMP PDE widely expressed in hematopoietic cells (*e.g.*, myeloid, lymphoid), non-hematopoietic cells (*e.g.*, smooth muscle, keratinocyte, endothelial), and sensory/memory neurons (32). The evidence for the PDE4 role in inflammatory response derives from different observations. It has been demonstrated that lipopolysaccharide selectively induces PDE4B2 mRNA expression in human circulating monocytes and PDE4A4 and PDE4B2 were detected at higher levels in peripheral blood monocytes of smokers (so with a possible continuous inflammatory stimulation) compared with non-smokers (33). Monocytes and macrophages are the main producers of the pro-inflammatory cytokine TNF whose levels decreased with PDE4 inhibition (34) and different studies show that production of TNF, IL-2, IL-4, and IL-5 and the proliferation of T lymphocytes are all dependent from PDE4 activity and, moreover, overexpression of PDE4 leads to an augmented inflammatory cytokines production (35). IL-12 production in macrophages, which is important for the differentiation of Th 1 cells, is also regulated by PDE4 (36). These evidences show that PDE4 is a key-enzyme in inflammatory response. On this basis, PDE4 inhibitors were proposed as therapy in different immune mediated diseases, including PsA.

Apremilast

Apremilast is a small molecule and a selective inhibitor of PDE4. It binds to the catalytic site of the PDE4 enzyme, thereby blocking cAMP degradation. Apremilast demonstrated to inhibit IL-2, IFNγ, IL-8, TNF production and different T-cell-derived cytokines *in vitro* (37). The efficacy and safety of apremilast in the treatment of psoriatic plaque were evaluated in two randomized phase 3 trials with comparable design. In ESTEEM 1 and ESTEEM 2, patients were randomized 2:1 to receive apremilast 30 mg twice daily or placebo for 16 weeks. The proportion of patients achieving a PASI-75 response was significantly greater ($P<0.0001$) in the apremilast-treated group than in the placebo group in both studies (38, 39). In PsA patients, four trials evaluated the efficacy and safety of apremilast. The PALACE 1 trial evaluated the efficacy and safety of apremilast in patients with active PsA with previous use of biologic therapy (40). In this trial, 504 patients were randomized to placebo, apremilast 20 mg twice daily, or apremilast 30 mg twice daily. At week 24, placebo treated patients were re-randomized to either the apremilast 20 mg arm or the apremilast 30 mg

arm. Of the 504 randomized patients prior use of a biologic was reported in 24% of patients. The primary efficacy endpoint was the proportion of patients achieving the ACR20 response at week 16, with significantly more patients achieving this endpoint in the apremilast 20 mg group (31%, P=0.0140) and in the apremilast 30 mg group (40%, P=0.0001) compared with placebo-treated patients (19%) (40). In this study, significant improvements in other secondary endpoints at week 24 were also noted with apremilast therapy (ACR50, ACR70 and physical functioning). Study discontinuation, because of adverse events, was comparable among groups (6% for apremilast 20 mg, 7% for apremilast 30 mg, and 5% for placebo) (40). The most frequently reported adverse events with apremilast were largely mild to moderate and dose-dependent. These included diarrhea, reported by 11 and 19% of patients in the apremilast 20 and 30 mg groups, respectively (*vs* 2% for placebo), and nausea, reported by 10% of apremilast 20 mg patients and 19% of apremilast 30 mg patients (*vs* 7% for placebo). These events presented early and were self-limiting, accounting for few study discontinuations. The 52-week results of the PALACE 1 trial demonstrated that in those patients who continued treatment with apremilast, treatment efficacy was mantained; ACR20 responses of 63 and 55% were reported in the apremilast 20 mg and apremilast 30 mg groups, respectively (41). Furthermore, apremilast was efficient in reducing the Maastricht ankylosing spondylitis enthesitis score, while none of the two doses significantly reduced C reactive protein levels and dactylitis score in respect to placebo at week 24 (40). No information was available regarding the efficacy of apremilast in axial disease or about the possibility to achieve a state of disease remission; however PALACE 2, 3 and 4 studies are still ongoing and will provide information on these aspects. On these bases, apremilast has been approved for the treatment of psoriasis and PsA.

CONCLUSIONS

Anti-TNF therapy showed its efficacy and safety in different rheumatic diseases and now a state of remission or low disease activity are achievable targets even in spondyloarthritis in general (42, 43) and in PsA (44-46). However, about 40% of patients lack to respond to TNF inhibitors. Fortunately, the treatment of PsA is rapidly evolving: beyond anti-TNF therapy, emerging novel therapies that target new molecules are rising. The discovery of the role of Th17 cells, the understanding of the role of the cytokines production together with the pathways involved in immune system activation, have made possible the develop-

Table I - Summary of efficacy of new approved drugs for psoriatic arthritis (data from randomized controlled trials).

		ACR20	ACR50	ACR70	PASI75	HAQ (mean change from baseline)
Ustekinumab 45 mg	24-week evaluation	42.4%	24.9%	12.2%	57.2%	–0.25
Ustekinumab 90 mg	24-week evaluation	49.5%	27.9%	14.2%	62.4%	–0.25
Secukinumab 150 mg	24-week evaluation	51%	35%	Not provided at 24 weeks	48%	Not provided at 24 weeks
Secukinumab 300 mg	24-week evaluation	54%	35%	Not provided at 24 weeks	63%	Not provided at 24 weeks
Apremilast 20 mg	24-week evaluation	26.4%	14.7%	5.5%	17.6%	–0.21
Apremilast 30 mg	24-week evaluation	36.6%	19.9%	10.6%	21%	–0.26

ACR, American College of Rheumatology; PASI, psoriasis area and severity index; HAQ, health assessment questionnaire.

ment of new drugs effective in treating PsA. Some of these agents are now available and their effectiveness on the various component of the disease seems to be similar in terms of ACR20 response (Table I) (47). Ustekinumab, secukinuamb and apremilast have been approved for PsA and, therefore, have been included in the recent EULAR update 2015 (48) and GRAPPA 2015 (49).

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