The Role of Tumor Necrosis Factor-α Blockers in Psoriatic Disease. Therapeutic Options in Psoriatic Arthritis

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ABSTRACT. Psoriatic arthritis (PsA) is a chronic inflammatory disease affecting peripheral and axial joints, usually associated with psoriasis (PsO) and involving various systems and organs (eye inflammation, such as uveitis; and involvement of nail and enthesis), and it usually requires a multidisciplinary treatment approach. Tumor necrosis factor-α (TNF-α) is overexpressed in psoriatic synovium and skin plaques and its selective inhibition by anti-TNF-α agents has been demonstrated to reduce TNF-α levels in the articular environment, reversing the synovial hyperproliferative phenotype. Studies performed on anti-TNF-α agents in PsA demonstrated that they are able to reduce neutrophil and macrophage infiltration as well as vascular cell adhesion protein 1 expression with ensuing synovial thickness normalization. The efficacy of anti-TNF-α agents for all PsA manifestations (peripheral arthritis, axial involvement, enthesopathy, and skin disease) suggests that anti-TNF-α efficacy might be related to the ability to influence angiogenesis and osteoclastogenesis, reduce synovial inflammation, and slow radiological disease progression. This review describes the role of anti-TNF-α in each manifestation of PsA. (J Rheumatol Suppl. 2015 Nov;93:73–8; doi:10.3899/jrheum.150642)

Key Indexing Terms:
PSORIATIC ARTHRITIS   PATHOGENESIS   ANTI-TUMOR NECROSIS FACTOR-α
CLINICAL RESPONSE   RADIOGRAPHIC PROGRESSION

Psoriatic arthritis (PsA) is a chronic inflammatory disease involving peripheral and axial joints, usually associated with psoriasis (PsO), an immune-mediated disease characterized by hyperproliferation and aberrant differentiation of keratinocytes. Because of its involvement of various systems and organs (peripheral arthritis, axial involvement, eye inflammation such as uveitis, skin and nail disease as well as enthesitis and dactylitis), psoriatic disease usually requires a multidisciplinary treatment approach.

A recent review by Chimenti, *et al*[1] underscores that the pathogenesis of PsA is still incompletely understood and the pathophysiological role of synovium has to be better elucidated.

Histologically, PsA is characterized by hyperplasia of the lining layer associated with a diffuse infiltrate of B and T cells, macrophages, dendritic cells, neutrophil proliferation, as well as increased angiogenesis. Oligoclonal T cell expansion has been demonstrated both in the skin and the synovium, associated with a high expression of monocyte-derived cytokines[1,2].

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According to these features, the role of tumor necrosis factor-α (TNF-α) appears to be intriguing. Specifically, TNF-α is overexpressed in psoriatic synovium and skin plaques, and its selective inhibition by anti-TNF agents has been demonstrated to reduce TNF-α levels in the articular environment, reversing the hyperproliferative phenotype of synoviocytes[2].

A peculiar feature of PsA is enthesitis, one of the criteria for the ClASsification of Psoriatic ARthritis (CASPAR)[3]. Lymphocyte and macrophage infiltrates are present at inflamed synovial-entheseal complexes, and chronic entheseal inflammation may lead to cystic and erosive changes at bone insertion of tendons, as well as spur formation, syndesmophytes, and periosteal new bone[1,2].

Studies on anti-TNF-α agents in PsA have demonstrated that they decrease neutrophil and macrophage infiltration as well as VCAM-1 (vascular cell adhesion molecule 1) expression, leading to synovial thickness normalization[1,2]. These data are considered the rationale underlying the clinical and radiological efficacy of anti-TNF-α agents in PsA.

The efficacy of anti-TNF-α agents in all manifestations of PsA has been described: It is argued that such efficacy might be related to the ability of these agents to modulate angiogenesis and osteoclastogenesis, thus reducing synovial inflammation and slowing radiological disease progression[1].

With these considerations in mind, we examine the role of anti-TNF-α biological agents in each manifestation of PsA. To date, 5 anti-TNF agents have proved effective in

PsA: Infliximab (IFX), a chimeric anti-TNF-α monoclonal antibody; adalimumab (ADA), a fully human anti-TNF-α monoclonal antibody; golimumab (GOL), another human anti-TNF-α monoclonal antibody; etanercept (ETN), a fusion protein consisting of the extracellular ligand-binding domain of the 75 kDa receptor for TNF-α and the Fc portion of human IgG1; and certolizumab pegol (CZP), a nanomolecule comprising a humanized Fab′ antibody fragment against TNF-α with a polyethylene glycol tail. With the exception of IFX, these agents are administered by subcutaneous injection and they have shown efficacy in PsA "across the board."[4,5,6,7,8].

ADA has been demonstrated to effectively decrease tender and swollen joint counts and to inhibit magnetic resonance imaging (MRI) articular changes (bone marrow edema, erosions, synovitis, and effusion) after 24 weeks of treatment. We recently reviewed the literature on ADA: Its efficacy in PsA has largely been confirmed on peripheral arthritis, enthesitis, dactylitis, and radiographic progression, both in randomized controlled trials (RCT) and in observational studies. Similarly, IFX efficacy has been demonstrated in observational studies, in RCT, and in longterm extension studies, with remission obtained in up to 24% of patients with peripheral PsA[1,6,7].

Significant efficacy of anti-TNF-α agents has also been demonstrated for ETN (PRESTA Trial[9]), as well as for GOL and CZP. Data from the GO-REVEAL RCT[10] showed that GOL treatment through 2 years was effective in maintaining clinical response [response rates: American College of Rheumatology 20% remission: 63%–70%; 28-joint Disease Activity Score (DAS28)-C-reactive protein (CRP): 77%–86%; Psoriasis Area Severity Index 75: 56%–72%] and inhibiting radiographic progression (mean change in PsA-modified Sharp/van der Heijde score) in GOL-treated patients: –0.36). No new safety signals were identified over 2 years of treatment[7,11]. Data on CZP have been obtained from RAPID-PsA, a 24-week phase III RCT: improvements in signs and symptoms of PsA, including joint and skin disease, enthesitis, dactylitis, and nail disease were demonstrated[7].

A large body of evidence supports the efficacy of anti-TNF-α agents in slowing radiographic progression. Hoff, *et al* in a pilot study showed that, in a subset of 120 patients from IMPACT II (Induction and Maintenance Psoriatic Arthritis Clinical Trial 2) in which cortical hand bone density was assessed at weeks 0, 24, and 54 by digital X-ray radiogrammetry on the same radiographs, hand bone loss in patients treated with TNF-α blocking agents was arrested[12,13,14]. Likewise, Poggenborg, *et al* in an MRI study showed that ADA could both reduce clinical signs of disease activity and avoid erosive progression in patients with PsA[15].

PsA-related enthesitis is known to be resistant to synthetic disease-modifying antirheumatic drugs (DMARD): both RCT and observational studies have shown that TNF-α blocking agents are beneficial in this regard. Genovese, *et al*

showed ADA efficacy in a placebo controlled, double-blind, randomized, multicenter study, where enthesitis score was significantly improved after 12 weeks of therapy[16]. Subsequently, these findings were confirmed by Gladman, *et al*[17]. Similar evidence of efficacy on enthesitis was reported by Sterry, *et al* for ETN in the PRESTA Study[9]; by Antoni and coworkers for IFX in IMPACT[12] and IMPACT2 trials[13]; and by Kavanaugh for GOL in the GO-REVEAL trial[10].

Greater efficacy of anti-TNF-α agents compared with synthetic DMARD has been demonstrated in dactylitis. In a longitudinal PsA cohort, the prevalence of dactylitis on at least 1 visit was 39%. Patients treated with biologics had better response to treatment compared with those treated with nonbiologic DMARD alone: multivariate analysis showed that only treatment type (anti-TNF-α agents vs DMARD) was a significant predictor of response of dactylitis at 12 months, with a relative risk of acute dactylitis taking DMARD versus biologics of 0.528 (95% CI 0.283–0.985, p = 0.045). The efficacy of anti-TNF-α on dactylitis is confirmed to be a class effect: ADA was confirmed effective in the ACCLAIM study[17]; ETN in the PRESTA study[9]; IFX in the IMPACT1[12] and IMPACT2[13] trials; and GOL in the GO-REVEAL trial[10].

Along the same lines, axial involvement, which is refractory to synthetic DMARD, has been shown to respond to TNF-α blockade in RCT (data from IMPACT[12,13] and ADEPT[18] trials[4,6,7,19]) and in observational studies[20,21,22,23,24,25,26,27,28].

Lubrano, *et al* investigated the effectiveness of ETN on axial manifestations of a group of patients with established PsA in a multicenter observational study that included 32 patients (median disease duration 14.5 yrs; 25th–75th percentiles: 9.2–17.00). Effectiveness of ETN was observed in 72% of patients for the Bath Ankylosing Spondylitis Disease Activity Index (p < 0.001), in 68% for the Bath Ankylosing Spondylitis Functional Index (p < 0.001), in 76% for erythrocyte sedimentation rate (p < 0.001), and in 68% of patients for CRP (p < 0.01)[20].

Overall, efficacy data have also been confirmed by systematic literature reviews[5,6,7] and observational studies from real-life cohorts (Table 1)[17,23-32].

On the basis of the published literature, numerous guidelines recommend anti-TNF-α agents for axial disease, as well as for peripheral arthritis, enthesitis, and dactylitis[4,5,6,8,21,22].

All these data are supported by many published RCT (Table 2A)[7,13,16,33-43,44,45,46,47]. No RCT have investigated the issue of switching between TNF-blocking agents, although it is recognized that a proportion of patients have to come off their first TNF inhibitor owing to inefficacy or side effects. The only exception is the RAPID-PsA study, which demonstrated the efficacy of CZP in active PsA where up to 40% of patients were anti-TNF failures[7]. Reports from observational cohorts have investigated the use of second and third-line drugs[4,5,6,7,8,16,23,24,25,26,27].

All published studies, although not always comparable in

Table 1. Efficacy data from observational studies in real-life cohorts.

Study[Reference]	Year	Method	Drug
Glintborg[29]	2011	Observational from registry data	Anti-TNF-α
Gladman[17]	2010	Open-label, observational study	Switch to ADA
Delaunay[23]	2005	Observational study	Switch from IFX to ETN
Saad[28]	2010	BSR registry; from 2002–2006, the BSRBR recruited pts starting anti-TNF therapies for PsA	Anti-TNF-α
Haberhauer[24]	2010	Observational study	Anti-TNF switching
Gomez-Reino JJ, BIOBADASER Group[30]	2006	Registry (2000–2004)	Anti-TNF
Fagerli[25]	2013	Registry (2001–2011)	Anti-TNF
Glintborg[31]	2013	DANBIO Registry	Anti-TNF
Van den Bosch[32]	2010	Prospective, open-label, uncontrolled study	ADA
Mazzotta[26]	2009	Observational study	ETN — SWITCH
Wick[27]	2005	Observational from the STURE registry	ADA — SWITCH

Anti-TNF: anti-tumor necrosis factor; ADA: adalimumab; ETN: etanercept; IFX: infliximab; BSR: British Society for Rheumatology; BSRBR: BSR Biologics Register; PsA: psoriatic arthritis; pts: patients.

terms of methods and sample sizes, indicate that the failure of an initial TNF-α antagonist does not preclude response to another. No data are yet available to indicate which TNF antagonist should be chosen after failure of a first anti-TNF-α agent.

According to published studies, switching to a second agent should be considered in patients who fail to respond adequately to a first TNF-α inhibitor[4,5,8,15,16,21,22,23,24,25,33]. Insufficient data are available about switching to a third, but this therapeutic approach is usually not recommended.

To date, efficacy and safety in PsA have also been demonstrated in RCT for biological agents other than TNF-α inhibitors, such as agents inhibiting the interleukin 17 (IL-17)[33] and IL-12/23 pathway (ustekinumab), which showed significant efficacy in patients with active PsA. In particular, ustekinumab was effective, both in TNF-α blocker-naive patients and in those previously treated with anti-TNF-α drugs, in reducing clinical disease activity (of both skin and joint involvement) and in slowing radiographic damage[1,2,7]. Therefore, ustekinumab could be considered as a treatment option for patients with active PsA and severe psoriasis who have failed to respond to anti-TNF-α agents.

Abatacept might have some efficacy in PsA, as shown by a phase II study, both in joint and skin disease, as well as in slowing radiographic disease progression as assessed by MRI[46]. Data are summarized in Table 2B.

On the other hand, rituximab induced modest improvement in PsA according to 2 open-label trials using data from a French registry on spondyloarthritides. Efficacy was more marked in patients who were naive to anti-TNF-α agents[48,49,50]. Regarding use of tocilizumab (TCZ) in PsA, so far most data are on axial disease; only case reports describe TCZ efficacy in PsA, and with conflicting results[50].

A phase II trial and a more recent phase III RCT in PsA demonstrated apremilast (phosphodiesterase type 4 inhibitor) efficacy compared to placebo[40].

According to published guidelines, in patients who fail to adequately respond to a TNF-α inhibitor, switching to another agent of the same class should be considered. However, for persistent inadequate response, other biological agents might be considered as second-line drugs, in particular, ustekinumab. Lastly, in patients who fail multiple therapies, potential third-line drugs to consider are abatacept and apremilast.

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Table 2A. Data from RCT on anti-TNF-α.

Author[Reference], Year	Method	Drug	Evaluated Items/Efficacy	Comments/ Limits
Van der Heijde[33], 2014	Phase III RCT	CZP	Radiographic progression (SHS)	Up to 40% of pts failed anti-TNF
Kavanaugh[34], 2013	Longterm extension	GOL	ACR response, DAS28-CRP response, PASI, dactylitis, MASES, SHS	No previous anti-TNF
Mease[7], 2014	Phase III RCT	CZP	ACR response, SHS, PsARC, PASI, Leeds Enthesitis Index, Leeds Dactylitis Index, and NAPSI	Up to 40% of pts failed anti-TNF
Torii[35], 2010	Phase III RCT	IFX	Peripheral arthritis and skin involvement evaluation	TNF-naive pts only
Antoni[36], 2008	Phase III RCT	IFX	ACR20/50/70, PASI, radiographic progression	TNF-naive pts only
Van der Heijde[37], 2007	Phase III RCT	IFX	Sharp/van der Heijde scoring method modified for PsA	TNF-naive pts only
Genovese[16], 2007	Phase III RCT	ADA	ACR and PsARC scores, PASI	TNF-naive pts only
Antoni[13], 2005	IMPACT trial, phase III RCT	IFX	PASI, ACR20/50/70 criteria, DAS28, ratings of enthesitis and dactylitis, and PsARC	TNF-naive pts only
Mease[38], 2004	Phase III RCT	ETN	ETN reduced joint symptoms, improved psoriatic lesions as well as inhibited radiographic progression	TNF-naive pts only
Mease[39], 2000	Phase III RCT	ETN	ETN offers pts with PsA and PsO a new therapeutic option for disease control	TNF-naive pts only

Table 2B. Data from RCT on biologics different from anti-TNF-α.

Author[Reference], Year	Method	Drug	Evaluated Items/Efficacy	Comments/Limits
Kavanaugh[40], 2014	Phase III RCT	Apremilast	Peripheral arthritis (ACR20/50/70), enthesitis (MASES), dactylitis, and skin involvement	Biologic-naive pts and pts who failed biologics
Kavanaugh[41], 2014	Phase III RCT	UST	ACR20, DAS28-CRP, PASI75, and PsA-modified SHS	Biologic-naive pts and pts who failed biologics
McInnes[42], 2014	Phase II proof-of-concept RCT	Secukinumab	Clinical responses, acute-phase reactant and quality of life improvements were greater with secukinumab versus placebo	TNF-naive pts only
Ritchlin[43], 2014	Phase III RCT	UST	ACR response, DAS28-CRP response, PASI score, dactylitis, enthesitis (MASES score), BASDAI	Both biologics-naive pts and biologics failures
McInnes[44], 2013	Phase III RCT	UST	Peripheral psoriatic arthritis (ACR response criteria)	TNF-naive pts only
Schett[45], 2012	Phase II RCT	Apremilast	ACR20/50/70 response, PsARC, EULAR response criteria based on DAS28	No highlighted differences between TNF-naive pts and those who failed TNF
Mease[46], 2011	Phase II RCT	ABA	ACR20 response, MRI scores for joint erosion, osteitis, and synovitis, PASI score	Phase II clinical trial, not applicable to real life
Gottlieb[47], 2009	Phase II RCT (2005-2007)	UST	Good efficacy in PsA pts (peripheral arthritis and skin disease)	Not highlighted if pts previously treated with TNF-α inhibitors had a different clinical outcome

RCT: randomized controlled trials; anti-TNF: anti-tumor necrosis factor; GOL: golimumab; IFX: infliximab; ADA: adalimumab; ETN: etanercept; CZP: certolizumab pegol; PsO: psoriasis; PsA: psoriatic arthritis; PASI: Psoriasis Area Severity Index; DAS28-CRP: 28-joint Disease Activity Score-C-reactive protein; MASES: Maastricht Ankylosing Spondylitis Enthesitis Scale; ACR20/50/70: American College of Rheumatology 20%-50%-70% improvement; PsARC: Psoriatic Arthritis Response Criteria; NAPSI: Nail Psoriasis Severity Index; SHS: Sharp/van der Heijde scores; UST: ustekinumab; ABA: abatacept; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; EULAR: European League Against Rheumatism; MRI: magnetic resonance imaging; pts: patients.

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