Anti-TNF-α therapy as an evidence-based treatment option for different clinical manifestations of psoriatic arthritis

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ABSTRACT

The development programmes of different TNF-blocking agents in psoriatic arthritis (PsA) not only provided substantial evidence for the therapeutic benefits of the specific treatment options, but also enabled new insights into the differential treatment effects on distinct disease manifestations. For the first time, specific robust evidence for distinctive effects on different manifestations of PsA, as a distinct entity separate from rheumatoid arthritis (RA), has been generated in a standardised way. The clearest evidence was shown for an effect on peripheral arthritis (polyarticular) with ACR20 response rates from 45 up to 58% (vs. 9–24% for placebo), and an inhibition of radiographic progression demonstrated for the first time for a treatment principle in PsA. However, as PsA does not remain confined to the peripheral joints, it was necessary to address diverse patterns of PsA-subtypes in the outcome measurements of the anti-TNF trials. Accordingly, the results of the clinical studies on anti-TNF treatment also have demonstrated efficacy on enthesitis, dactylitis and skin psoriasis, either in sub analysis of results from phase III RCTs, or in additional prospective studies.

Introduction

The development of the TNF-blockade as a treatment principle has provided a new era of evidence for therapeutic effectiveness in psoriatic arthritis (PsA), as a distinct entity apart from other rheumatic diseases. In past times, conventional synthetic DMARD-therapies for PsA-treatment were mainly based on evidence originally derived from clinical studies in rheumatoid arthritis (RA) (with the exception of SASP (1)). Anti-TNF-α treatment in PsA was developed as a separate indication for PsA, and thus independent of the pre-existing data in RA.

The performance of PsA-specific clinical studies was limited by the absence of specific validated outcome criteria for PsA. For many years, the composite of PsA response criteria set (PsARC (2)) was the only available specific outcome measurement for PsA available to demonstrate effectiveness in clinical trials. Suitable PsA-specific outcome tools were lacking for other clinical manifestations of the multi-faceted disease including dactylitis, enthesitis, axial disease, impairment of life quality, etc. Therefore, clinical trials in PsA were mainly designed to demonstrate differences between active compound and placebo in (polyarticular) peripheral arthritis by adopting outcome criteria from RA studies (*e.g.* ACR responses or DAS28). As a consequence, best evidence was generated for polyarticular ("RA-like") manifestations of PsA, due to a bias for study inclusion of patients with a high mean score of swollen and tender joints (almost always more than 5), often not reflecting disease characteristics of patients in routine clinical care. Power calculations for other relevant manifestations such as enthesitis, dactylitis, axial involvement or skin disease, remained neglected in early anti-TNF trials for PsA. Accordingly, these studies could provide evidence only for pharmacological effect on these PsA sub phenotypes by chance, in case sufficiently high numbers of patient were available for subgroup analysis.

The definition of disease modifying anti-rheumatic drugs (DMARDs) requires more than just control of signs and symptoms, but also evidence of reduction or prevention of joint damage and preservation of the structure and function of the joints (3). Anti-TNF-α agents could fulfil these DMARD-criteria in relation to PsA for the first time. In the present article, an overview will be provided of TNF-α as a target in

PsA-therapy, as well as of the efficacy of the licensed anti-TNF-α agents currently available. Evidence from phase III randomised clinical trials (RCTs) in active PsA for the main outcome criteria at the defined primary endpoints will be discussed. In addition, available evidence for the efficacy of anti-TNF-α agents for changes in signs and symptoms of other PsA manifestations like enthesitis, dactylitis and skin psoriasis will be presented. We refer to the actual ASAS recommendations (4) for the treatment of axial manifestations of PsA.

TNF-α as valuable target for therapy of distinct manifestations of PsA

TNF-α is a pro-inflammatory cytokine associated with pleiotropic effects on different cell-types (5). It is produced predominantly by macrophages, but also by other cell types involved in inflammation, such as CD4+ lymphocytes, NK cells, neutrophils, mast cells and others are also relevant sources. During the inflammatory process, it is overexpressed in two different forms: the soluble TNF-α (sTNF-α) and the transmembranous form (tmTNF-α). Both forms act differently within this process: tmTNF-α requires cell-to-cell contact to function, whereas sTNF-α acts at sites without contact to the TNF-α-producing cells (6).

Two different levels of TNF-α function can be distinguished: At a cellular level, TNF-α plays a role in lymphocyte and neutrophil adhesion, inhibition of haemopoiesis, stimulation of prostaglandin E$_2$ synthesis, and the production of other (pro-inflammatory) cytokines. At the target tissue level, TNF-α participates locally in catabolic events, such as proteoglycan breakdown, acute tubular necrosis and bone resorption (7, 8). Thus, TNF-α is involved in a number of biological processes that contribute to joint damage (including stimulation of bone resorption, inhibition of bone formation and proteoglycan synthesis as well as induction of collagen and cartilage degrading metalloproteinases) (9-12).

The pro-inflammatory intracellular signalling cascade is initiated upon interaction of TNF with its specific cell-membrane anchored receptor. Two almost ubiquitously expressed, structurally similar but functionally distinct TNF-α receptors can be distinguished: TNF Receptor 1 (TNFR1, synonymous: p55) and TNF Receptor 2 (TNFR2, synonymous: p75). These receptors form dimers on the cell surface, thereby binding to a trimeric TNF-α molecule to induce signal transduction (7).

Soluble forms of both, p55 and p75 TNF-receptor have been identified in sera and synovial fluids of patients with rheumatic diseases. Results of studies suggest that they may act as endogenous TNF-α inhibitors (13-16). Synovial fluid analysis has demonstrated that levels of TNF-α are significantly higher in patients with PsA compared to those with osteoarthritis, but lower than in patients with RA-derived joint effusions, whereas TNF-α is undetectable in sera and synovial fluid from healthy humans (17-19). Overall, the best evidence for a role of TNF-α in joint inflammation and destruction is the capacity of TNF-α inhibitors to improve clinical symptoms and disease activity in certain forms of inflammatory arthritis and slowing or stopping progression of clinical and radiographic joint damage.

Different TNF-α inhibitors

At this time (August 2015), five different TNF-α inhibitors have been licensed for the treatment of PsA, with and without concomitant use of methotrexate: adalimumab, certolizumab, etanercept, golimumab and infliximab. In contrast to RA, a benefit of the additional use of methotrexate in anti-TNF-α therapy has not been documented from randomised clinical trials in PsA. In a systematic literature search, no benefit on clinical efficacy for the combination therapy with methotrexate was detected despite a prolonged drug survival of monoclonal anti-TNF antibodies (20). Randomised clinical trials should be performed to address this topic.

Infliximab is a chimeric, humanised, mouse anti-TNF-α monoclonal antibody consisting a murine variable region and a human IgG1 constant region. Infliximab binds to both the monomeric and trimeric forms of soluble TNF-α (21). Infliximab forms stable complexes with soluble TNF-α. Each infliximab molecule is capable of binding to two TNF-α molecules, and up to three infliximab molecules can bind to each TNF-α homotrimer. In PsA, infliximab is administered intravenously after a loading phase (week 0, 2, 6) every 6 to 8 weeks, at a dose of 5 mg/kg per body weight. Due to the intravenous administration, infliximab circulates at high initial concentrations in serum that are 13- to 40-fold greater than the peak concentrations of adalimumab or etanercept at steady state (22). Due to its structure with a murine-derived TNF binding antibody-region, infliximab is the anti-TNF-agent with the highest probability for the formation of neutralising anti-drug antibodies and thus the highest risk of anaphylactic reactions (23).

Adalimumab and golimumab are fully humanised anti-TNF-alpha monoclonal antibodies (mAb), which are similar to normal IgG1. Adalimumab is administered at 40 mg subcutaneously every other week, golimumab at 50 mg every four weeks.

Etanercept is a TNF-α receptor Fc fusion protein that binds to TNF-α and lymphotoxin. Therefore, its structure combines an extracellular portion of the human TNF-R2 (p75 TNF receptor) linked to the Fc portion (CH2 and CH3 domains) of human IgG1. Etanercept is thought to form 1:1 complexes with TNF-α trimer only and the complexes are relatively unstable compared with those formed with infliximab (20). Etanercept is administered once (50 mg) or twice weekly (25 mg), subcutaneously. Peak plasma concentrations are reached 48 to 60h after administration (24); the volume of distribution at steady state is at least as high as that for infliximab or adalimumab, which implies comparable or greater tissue penetration for etanercept. In clinical use, etanercept shows a lack of efficacy in the treatment of granulomatous diseases, such as Crohn's disease and Granulomatosis with polyangiitis (25, 26) and is less effective in the therapy of psoriatic skin disease compared to infliximab or adalimumab (27, 29). Nevertheless, autoantibody formation occurs, but less often during treatment with etanercept compared to adalimumab or infliximab (30, 31).

Table I. Overview of biochemical and clinical reponses to anti-TNF-α therapies.

	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab
Class	mAb	Fc-Fusion protein	mAb	mAb	mAb fragment
Structure	chimeric (murine-human)	human	human	human	peg human
TNF ligands	sTNF, tmTNF	sTNF, tmTNF	sTNF, tmTNF	sTNF, tmTNF	sTNF, tmTNF
tmTNF binding	+++	++	+++	No data available	+++
Administration	IV 5mg/kg per body weight every 6 to 8 weeks	SC 50mg once weekly 25mg twice weekly	SC 40mg every other week	SC 50mg every 4 weeks	SC 200mg every other week 400mg every 4 weeks
Immunogenicity Monotherapy	+++	+	+	+	+
Effectiveness on Psoriasis (skin)	+++	++	+++	+++	+++
RCTs	IMPACT (41) IMPACT2 (42)	Mease *et al.* (44, 45)	ADEPT (47) Genovese *et al.* (48)	Go-REVEAL (50)	RAPID-PsA (51)

mAb: monoclonal antibody; IV: intravenous; SC: subcutaneous.

Certolizumab is a Fab fragment of an anti-TNF-α IgG1 mAb. Thus the Fab-domain is lacking the Fc portion, and instead is covalently attached to two cross-linked 20 kDa chains of poly-ethylene glycol. Due to its structure with only a single Fab domain, certoli-zumab should not have the capacity to crosslink tmTNF. However, it has been found to induce reverse signalling in cells leading to tmTNF inhibition (32). Infliximab, adalimumab, etanercept and certolizumab pegol bind equally well to tmTNF-α on tmTNF-α-transfected cells (32), but exhibit weaker affini-ties compared to their interactions with sTNF-α (33).

In studies of safety, all of the anti-TNF-agents increase the overall risk of infec-tions (34, 35), particularly reactivation of tuberculosis (35, 36). Etanercept with its reduced effect on granuloma-tous diseases appears to be associated with a lower risk for reactivation of tuberculosis compared to mAbs (37). The potential threat of a weakened im-munosurveillance of malignancies by TNF-blocking agents has been care-fully monitored in respective registries. Increased rates of lymphoma were ini-tially reported in patients treated with TNF-α inhibitors (38). However, there is evidence that the severity of the ac-tive underlying immune-mediated dis-ease is responsible for the increased lymphoma risk in RA, independent from its therapy (39, 40). Non-melano-ma skin cancer (NMSC) also appears to

Table II. Overview of approval status of anti-TNF-α therapies for psoriatic arthritis and psoriasis.

Substance	Approved for PsA	Approved for Pso	Effectiveness on Skin from PsA studies
Infliximab	yes	yes	PASI 75 (week 14): 64% (42)
Etanercept	yes	yes	PASI 75 (week 24): 23% (45)
Adalimumab	yes	yes	PASI 75 (week 48): 58% (55)
Golimumab	yes	no	PASI 75 (week 14: 40% (50)
Certolizumab	yes	no	PASI 75 (week 24): 47% (51)

be associated with anti-TNF-α therapy, especially when the patient has been previously treated with phototherapy for skin psoriasis (41). Other adverse events that are associated with anti-TNF-α treatment include systemic lu-pus erythematosus-like syndromes and demyelinating diseases (42).

Evidence for efficacy of different anti-TNF-α agents
Infliximab
The efficacy and safety of infliximab in active PsA was documented in two major placebo-controlled randomised clinical trials (RCTs), the IMPACT study (43) and the IMPACT 2 study (44). In these studies, doses of 5 mg/kg per body weight were compared with placebo in more than 300 patients in a randomised setting. The primary end-point of the IMPACT study was the ACR20 response at week 16, which was seen in 45% of the patients in the infliximab-treatment group compared with 10% in the control group. In IM-PACT 2, infliximab treatment resulted

in an ACR20 response in 58% of the patients at week 14 (primary endpoint IMPACT 2) compared with 11% of control patients. The PsARC response criteria were met in 75% (IMPACT) and 77% (IMPACT 2) of infliximab-treated patients compared with 21% and 27% of control patients. Accord-ing to the chosen primary endpoints, infliximab showed highly significant changes in comparison to placebo. In addition, in these studies, infliximab demonstrated high capacity to inhibit radiographic progression as well as ef-ficacy against enthesitis and dactylitis. A significant reduction of PASI was re-ported in the PsA-RCTs but also from Psoriasis RCTs (45).

Etanercept
The efficacy and safety of etanercept in active PsA was reported by Mease *et al.* (46, 47) in two major placebo-controlled randomised clinical trials (RCTs) which included more than 260 patients. Etanercept was administered subcutaneously using a dose of 25mg
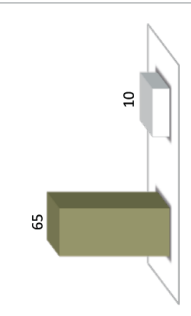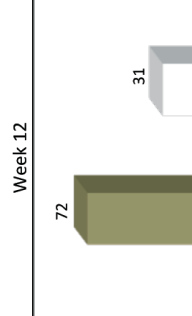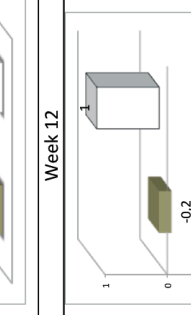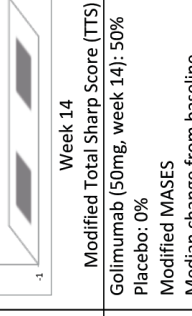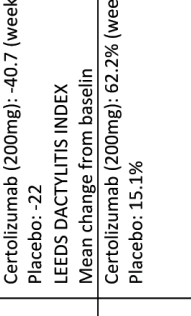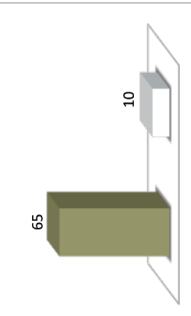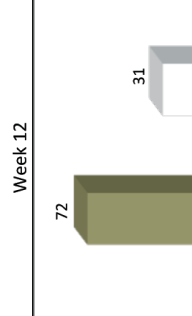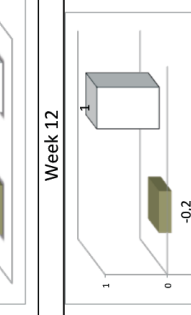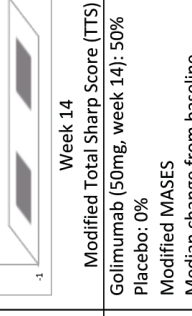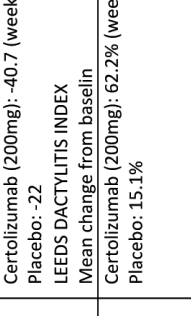
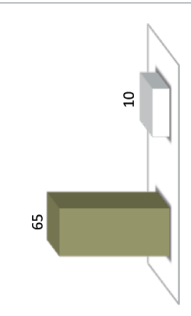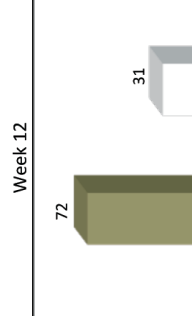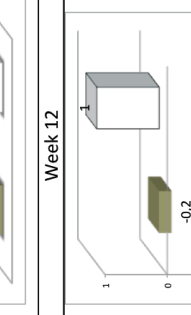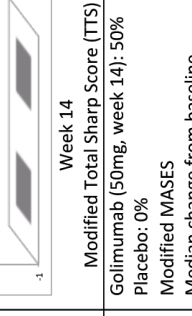|	Infliximab (IMPACT[41])	Etanercept (Mease et al.[44], PRESTA[46])	Adalimumab (ADEPT[47])	Golimumab (Go-Reveal[50])	Certolizumab (RAPID-PsA[51])
ACR20 response [%]	65 / 10 — Week 16	59 / 15 — Week 12	58 / 14 — Week 12	51 / 9 — Week 14	58 / 24 — Week 12
PSARC response [%]	75 / 21 — Week 16	72 / 31 — Week 12	62 / 26 — Week 12	73 / 21 — Week 14	78,3 / 33,1 — Week 24
Radiographic Progression	W24: 0,82 / −0,7; W54: 0,53 / −0,94 — Weeks 24 and 54 Modified TTS	−0,03 / 1 — Week 12 Total Sharp Score (TTS)	−0,2 / 1 — Week 12 Modified Total Sharp Score (TTS)	−0,09 / 0,27 — Week 14 Modified Total Sharp Score (TTS)	No progression in mTTS more common than in placebo group p<0,001 — Week 24 Modified Total Sharp Score (mTSS)
Enthesitis	Infliximab: 22% (W14), 20% (W24) Placebo: 34% (W14), 37% (W24) % of patients with enthesitis	Etanercept (PRESTA): 73.7% (week 12) IMPACT Index % improvement to Baseline	ADEPT: improvement in ADA-group but no significant changes IMPACT Index	Golimumab (50mg, week 14): 50% Placebo: 0% Modified MASES Median change from baseline	Certolizumab (200mg): −2 (week 24) vs Placebo: −1.1 LEEDS Enthesitis Index LEI mean change from baseline
Dactylitis	Infliximab: 18% (W14), 12% (W24) Placebo: 30% (W14), 34% (W24) No of patients with ≥ 1 dactylitis digit (%)	Etanercept (PRESTA) 74.3% (weeks 12) scored 0-3 % improvement to baseline	ADEPT: n.s. Gladman et al.: significant change % of dactylitis in ≥4 digits of hand and feet	Golimumab (50mg, week 14): 76% Placebo: 0% No of patients with dactylitis/no assessed (%); median change from BL	Certolizumab (200mg): −40.7 (week 24) Placebo: −22 LEEDS DACTYLITIS INDEX Mean change from baselin
Skin PASI75	Infliximab (week 16): 86% Placebo: 12%	Etanercept (week 12): 23% Placebo: 3%	Adalimumab (week 24): 59% Placebo: 1%	Golimumab (50mg): 40% (week 14) Golimumab (100mg): 58% (week 14) Placebo: 3%	Certolizumab (200mg): 62.2% (week 24) Placebo: 15.1%

Fig. 1. Overview of efficacy of the different anti-TNF-α-therapies.

twice weekly. Significant relief at week 12 (primary endpoint ACR20 response) was demonstrated with an ACR20 response in 58% in the etanercept group compared with 15% in patients control and a PsARC response of 72% (etanercept) compared with 31% in the control group. Inhibition of radiographic progression also was greater in patients treated with etanercept versus control patients. No significant efficacy was reported for enthesitits and dactylitis in these RCTs. However, in subsequent PRESTA-study (48), in which administration of 50 mg once weekly was compared with a dose of 50 mg etanercept twice weekly over a 6 month observational period (no placebo control), improvement was demonstrated in dacytilitis and enthesitis. A significant reduction of PASI was reported in the PsA-RCTs as well as in psoriasis RCTs (45).

Adalimumab
The efficacy and safety of adalimumab in active PsA was reported in the ADEPT-study (48) and by Genovese *et al.* (49), including more than 400 patients. Adalimumab was administered at 40mg every other week, subcutaneously. The ACR 20 response, one of the primary endpoints, was met at week 12 in 58% of the patients taking adalimumab and in 14% of control patients. In the Genovese *et al.* study, 39% of the patients in the adalimumab group met ACR20 criteria *versus* 16% in the control group. Adalimumab also resulted in significant inhibition of radiographic progression compared with a control group at week 24. A trend towards a reduction of disease severity, of enthesitis and dactylitis was seen, but was not statistically significant. In addition, openlabel study by Gladman *et al.* (51) documented a favourable effect on reduction of dactylitis. Significant reduction of PASI was reported in the PsA-RCTs as well as the psoriasis RCTs (45).

Golimumab
Golimumab was documented to have efficacy in more than 400 patients with PsA in the Go-Reveal placebocontrolled RCT (52). Two doses (50mg and 100 mg every 4 weeks) were tested. The pooled response to golimumab

for the primary endpoint at week 14, ACR 20 response, was met in 49% of all patients, 51% at 50mg dose, 45% at 100mg dose compared to 9% in the placebo group. A significant improvement in the enthesitis score was observed at both dosages. No significant differences between placebo and golimumab were seen in dactylitis scores at weeks 12 and 24 for 50 mg, but a significantly greater improvement in severity score was reported at a 100mg dose. A significant reduction of PASI was reported from in the PsA-RCTs as well as the psoriasis RCTs (45).

Certolizumab pegol (Cimzia®)
Certolizumab pegol, as the pegylated anti-TNF-α-Fab fragment was efficacious with regard to the primary endpoint, ACR20 response at week 12, of the RAPID-RCT performed in more than 400 patients with active PsA (53). Certolizumab was administered at a loading dose of 400 mg at weeks 0, 2 and 4 followed by 200 mg every 2 weeks or 400 mg every four weeks. ACR20 was met by 58% of the patients in the 200 mg dose group and by 51.9% in the 400 mg treatment group, compared with 24.3% in the control group. A statistically significant response, in enthesitis and dactylitis, was seen at week 24. A significant reduction of PASI also was reported in both treatment groups in PsA-RCTs and psoriasis RCTs (45). Moreover, in a sub-group analysis within the study, certolizumab demonstrated comparable efficacy to that of the anti-TNF-α therapy to which the patients had been exposed previously.

Summary
TNF-α inhibitors are the first drugs to be approved for PsA, showing significant efficacy in RCTs, not only in peripheral arthritis, but also in inhibiting radiographic progression, dactylitis, enthesitis and skin psoriasis. The evidence level for the primary outcome (ACR20 response rate) was comparable for each compound, although, some differences were noted for extraarticular manifestations of PsA, primarily due to the different study designs and numbers of patients included over time. Additionally, in an indirect com-

parison, no relevant differences could be demonstrated between the different treatments (54). In a recently published update for GRAPPA review, the number of patients needed to treat to achieve ACR20 response for peripheral arthritis, was estimated as 3 for each of the licensed anti-TNF-α agents (55).

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