Psoriatic arthritis: treatment strategies using biologic agents

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SUMMARY

The traditional management of psoriatic arthritis (PsA) includes NSAIDs, corticosteroids and DMARDs. Advancement in the knowledge of the immunopathogenesis of PsA has been associated with the development of biologic agents which have revolutionized the management of the disease. Among biologics drugs, there are the 4 currently available anti-TNFα blocking agents (etanercept, infliximab, adalimumab and golimumab) which are more effective than traditional DMARDs on symptoms/signs of inflammation, quality of life, function, and in inhibiting the progression of the structural joint damage. Despite of the high cost, TNF inhibitors are cost-effective on both the musculoskeletal and skin manifestations of psoriatic disease.

Key words: *Psoriatic disease, psoriatic arthritis, therapy, biologic drugs, anti-TNFα agents*

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INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease involving musculoskeletal structures such as joints, entheses, the synovial sheaths of tendons and the axial skeleton together with the skin and nails and showing different clinical phenotypes and course (1). In 2006, a new designation has been proposed with the aim to cover all these clinical situations: psoriatic disease (2).

In earlier times, PsA was considered a mild disease. In the last three decades, evidence has been collected that PsA is erosive and deforming in 40-60% of patients with joint damage emerging in the first years of the disease onset (3-8). Patients with PsA suffer from diminished quality of life (QoL) and functional impairment and have a significant escalation in mortality compared to the general population (9, 10).

Therapies for PsA have been insufficient until some years ago (11). Recent advancement in the knowledge of the immunopathogenesis of PsA has been associated with the development of biologic agents. The anti-tumor necrosis factor α (TNFα) agents (etanercept, infliximab, adalimumab and golimumab) have opened new horizons. These drugs moderate signs and symptoms of inflammation, improve QoL and functional status, and inhibit the progression of structural destruction in peripheral joints (12-15).

In view of the fact that nowadays drugs able to modify the course of PsA are available, the disease should be early diagnosed and treated. Truly, the major goals of the management, i.e. the decrease of pain intensity, the improvement of function and the prevention of joint injury, can be better achieved by early intervention (16-20).

RATIONALE FOR USE OF BIOLOGICS

Recent advancement in the knowledge of the immunopathogenesis of PsA has permitted the development of novel drugs including new TNFα blockers, interleukin 1, 6, 12, 23 and 17 inhibitors, co-stimulator modulation inhibitors, B cell depleting agents, small molecules and RANK/RANKL inhibitors (21). However, TNF inhibitors are currently the only approved biologic agents for the treatment of PsA.

Several findings have showed the role of the pro-inflammatory cytokine TNF-α in

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the pathogenesis of PsA providing the rationale for the use of anti-TNF agents. *In situ* hybridisation studies have showed the presence of TNF-α in psoriatic skin, in the synovium of clinically involved joints and in inflamed entheses. Conversely, cell infiltration in affected skin and joints appears to decrease after TNF-α inhibition (22).

APPROVED BIOLOGIC TREATMENT

Biologic drugs used in PsA include the anti-TNFα biologic agents etanercept, infliximab, adalimumab and golimumab. All four currently available TNFα blockers have been studied in randomized controlled trials (RCTs) and in observational post-marketing studies with consistent evidence supporting their safety and efficacy in patients with PsA (23-25). A recent systematic literature review evaluated treatment efficacy and safety observed during 8 RCTs of anti-TNF agents (3 of infliximab, 2 of etanercept, 2 of adalimumab, and 1 of golimumab) compared with placebo in patients with active PsA (24). At 12-14 weeks, all four TNF inhibitors were significantly more effective than placebo for PsA Response Criteria (PsARC), American College of Rheumatology (ACR) 20, 50 and 70 response criteria and Psoriasis Area and Severity Index (PASI) (Table I). Some trials also showed an effect on dactylitis and enthesitis (24). Additionally, the anti-TNF agents have been shown to significantly improve measures of fatigue, function and quality of life (25). No different safety problems from those observed in patients with rheumatoid arthritis have been reported in those with PsA (24). However, although the occurrence is infrequent, TNF inhibitors are associated with an increased risk of bacterial, viral, invasive fungal and mycobacterial infections, making careful monitoring and early evaluation critical.

Data from registry-based longitudinal studies confirmed the effectiveness and long-term safety of anti-TNF therapies in a real life setting (26, 27). Additionally, anti-TNF therapies are the first with proven efficacy in slowing down or halting radiographic progression (27).

To date, there is no direct head-to-head randomised controlled trial comparing anti-TNF agents. However, by an indirect analysis of placebo-controlled trials no significant differences in the proportion of patients achieving PsARC and ACR 20 or experiencing serious adverse events seem to emerge (23, 24). As far as skin involvement is concerned, there is evidence for a poor PASI 75 response at 12 weeks for etanercept when compared with the other anti-TNF agents (24). Since no specific anti-TNF agent has been demonstrated to be more effective than others, the drug choice should be made according to the available safety data, the presence of extra-articular manifestations and the patient's preferences. Indicatively, patients with PsA and uveitis or inflammatory bowel disease should be preferentially treated with a monoclonal antibody, whereas patients at risk of tuberculosis should preferentially receive etanercept.

At present, no RCT has been purposely carried out to assess the effectiveness of any anti-TNF therapy in PsA patients with manifestations different from peripheral joint involvement. With regard to spinal disease, only one observational study reported on the effect of etanercept in 32 patients with axial PsA (29). After a 12-month

Table I - Efficacy comparison for currently approved TNF inhibitors.

TNF inhibitor (reference)	ACR 20 (week 12 or 14)	PsARC (week 12 or 14)	PASI 75 (week 24)
Adalimumab (14)	58%	62%	59%
Etanercept (12)	59%	72%	23%
Golimumab (15)	51%	73%	56%
Infliximab (30)	58%	77%	60%

Data are only presented for an illustrative purpose not for a direct comparison

treatment, a significant improvement of BASDAI was observed in 72% of patients and of BASFI in 68% (29). Dactylitis and enthesitis were evaluated as secondary end points in some RCTs on golimumab (15) and infliximab (30, 31). A significant improvement was observed in these studies.
Although there are only few data from registries and observational studies on switching from one TNF-α inhibitor to another in PsA (32-34), PsA patients who do not respond or do not tolerate a TNFα blocker are successfully treated with another in clinical practice. The implementation of treatment strategies after failure of one biological agent is needed and, therefore, a preference for a particular TNF inhibitor cannot be established. However, in case of discontinuation due to lack of efficacy, it would be logical to switch to a TNF-α blocker structurally different from the one which failed.

Infliximab is a chimeric (mouse-human) monoclonal antibody specific for soluble and membrane-bound TNFα infused at a dosage of 5 mg/kg body weight over a period of at least 2 hours at weeks 0, 2, and 6 and every 8 weeks thereafter.
The efficacy of infliximab has been mainly evaluated in the IMPACT 2 trial enrolling 200 patients with active PsA despite the use of previous DMARDs or NSAIDs (30). The 14-week data showed that, compared with placebo, infliximab-treated patients had significantly better response rates for ACR 20 (58% *vs* 11%), PsARC (77% *vs* 27%), and PASI 75 (64% *vs* 2%). When compared with the placebo group, fewer patients in the infliximab group had dactylitis (18% *vs* 30%) or active enthesopathy (22% *vs* 34%). Disability and quality of life measures were also significantly improved by infliximab treatment compared with placebo. Infliximab was generally well tolerated, with a similar incidence of adverse events in each group (30).
By using the PsA modified Sharp score, infliximab showed to inhibit radiographic progression. At week 54, mean changes from baseline in PsA modified Sharp score were -0.94 in patients randomized to receive infliximab and +0.53 in those receiving placebo/infliximab (35).
During a 2-year study, infliximab was generally well tolerated, with serious adverse events and infusion reactions occurring in 5% of the patients (36).
Etanercept is a soluble TNF receptor p75-IgG1 fusion protein that is administered subcutaneously, either as a single 50 mg weekly dose or as two 25 mg doses given 3-4 days apart.
The efficacy of etanercept in patients with PsA was firstly assessed in the trial by Mease et al. that enrolled 205 patients with active PsA despite the use of previous NSAIDs (12). Compared with placebo, patients treated with etanercept 25 mg twice weekly showed significantly better response rates for ACR 20 (59% *vs* 15%) and PsARC (72% *vs* 31%) at 12 weeks, and for PASI 75 (23% *vs* 3%) at 24 weeks. Disability, as measured by the HAQ, decreased significantly in the etanercept group. Etanercept was well tolerated in this study as proved by similar proportions of patients with adverse events and infections in the 2 groups (12).
Etanercept also succeeded in inhibiting radiographic disease progression. At 12 months, the mean annualized rate of change in the modified total Sharp score was -0.03 unit in the etanercept group compared with +1.00 unit in the placebo group (12).
The clinical efficacy and good safety profile of etanercept found in RCTs have also been confirmed in a number of open long-term studies (37, 38).
Adalimumab is a fully human anti-TNFα monoclonal antibody given at the dosage of 40 mg subcutaneously every other week.
The efficacy of adalimumab in patients with PsA was firstly assessed in the ADEPT trial that enrolled patients with moderately to severely active PsA despite the use of previous NSAIDs (14).
The 12-week data showed that patients treated with adalimumab 40 mg had significantly better response rates for ACR 20 (58% *vs* 14%), PsARC (62% *vs* 26%), and PASI 75 (49% *vs* 4%) compared with placebo. Disability and quality of life measures were also significantly improved

with adalimumab treatment. Adalimumab was generally safe and well-tolerated during this trial with a similar incidence of adverse events compared with that in the placebo group (14).
As far as radiographic progression is concerned, the mean change at week 48 from baseline in the modified Sharp score was 0.1 in patients receiving adalimumab for 48 weeks and 1.0 in those receiving placebo for 24 weeks followed by adalimumab for 24 weeks (39).
During a 2-year open label extension study, adalimumab showed a good safety profile with no clinically meaningful changes in the occurrence of adverse events (40).
Golimumab is a fully human IgG1k anti-TNFα antibody generated and affinity-matured in an *in vivo* system to obtain high affinity and specificity for human TNFα. Golimumab is currently given by subcutaneous injection (50 mg every month), but intravenous administration will be available in future. Its serum half-life was estimated at 2-3 weeks, providing basis for the less frequent administration (monthly) compared to other available subcutaneous TNFα antagonists.
The main clinical data were derived from the GO-REVEAL trial that compared golimumab with placebo for the treatment of patients with active PsA despite the use of previous DMARDs or NSAIDs (15). The 14-week data showed that golimumab 50 mg significantly improved ACR 20 (51% *vs* 9%), PsARC (73% *vs* 21%), and PASI 75 (40% *vs* 3%) compared with placebo. Significant improvement was observed for other major secondary endpoints including HAQ, SF-36, NAPSI, and PsA-modified MASES index. Golimumab was generally well tolerated in this trial (15). The open-label extension of the study showed that these beneficial effects were also maintained at 104 weeks. Until now these data have been published only as an abstract (41).
Additionally, PsA patients receiving golimumab showed significantly less progression of the structural joint damage at week 52 of treatment in comparison with those receiving placebo (42).

RECOMMENDATIONS FOR THE USE OF BIOLOGICS IN CLINICAL PRACTICE

An improvement of the prognosis of PsA can be achieved not only by therapeutic advances (i.e. anti-TNF-α agents), but also by a better standardization of the management of the disease.
It has been estimated that a physician would need to read about 20 journal articles a day to keep abreast of all research relevant to a particular area of interest (43).
This is clearly complicated. For this reason in the recent years a growing attention has been focused on the use of synthesized evidence resources such as systematic reviews, meta-analyses, and evidence-based clinical practice guidelines and recommendations.
Within the field of research in PsA, there has been an increasing interest in proposing new sets of recommendations for the management of the disease.
Several international and national recommendation sets are currently available for PsA management. GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) (Table II) (11, 44) and EULAR (European League Against Rheumatism) (Table III) (45) recommendations address all pharmacological therapies while the Italian Society for Rheumatology (SIR, Società Italiana di Reumatologia) recommendations (Table IV) (46) are purposely designed to help Italian rheumatologists in everyday clinical practice management of PsA patients treated with biologic therapy.
All these recommendations suggest that anti-TNF therapies should be reserved for patients with active disease and in general include quite similar criteria (Tables II, III, IV) for starting the biologic agent in each pattern of presentation of the psoriatic disease i.e. peripheral arthritis, axial disease, enthesitis and dactylitis.
Active disease was generally defined as one or more tender and inflamed joint and/or tender enthesis point and/or dactylitic digit and/or inflammatory back pain.

Table II - GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) recommendations for starting TNF inhibitors in patients with active psoriatic arthritis.

Peripheral arthritis	Axial disease	Enthesitis	Dactylitis
• Moderate to severe forms • Failure to at least two DMARDs administered alone or in combination for at least 3 months • Patients with poor prognosis could be considered for TNF • Inhibitors even if they have not failed a standard DMARD • Factors associated with a poor prognosis: polyarticular disease; elevated ESR; failure of previous medication trials; the presence of damage, either clinically or on x-ray; loss of function as assessed by HAQ; diminished QoL as assessed by SF-36, Dermatology Life Quality Index (DLQI), or PsAQoL	• Moderate to severe forms • Failure to NSAIDs • BASDAI >4	• Severe forms (loss of function or > 2 sites and failure of response (NSAIDs, physical therapy, corticosteroids, DMARDs)	• Failure of response (NSAIDs, corticosteroids, DMARDs)

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index

Table III - EULAR (European League Against Rheumatism) recommendations for starting TNF inhibitors in patients with active psoriatic arthritis.

Peripheral arthritis	Axial disease	Enthesitis	Dactylitis
• Inadequate response to at least one synthetic DMARD • Evidence of active arthritis in terms of swollen joints and/or at least moderate disease activity by a composite disease activity measure and/or active disease with impaired function or quality of life • Exceptionally, very active patient naive of DMARD treatment (particularly those with many swollen joints, structural damage in the presence of inflammation, and/or clinically relevant extra-articular manifestations, especially extensive skin involvement)	• Insufficient response to NSAIDs • BASDAI ≥4	• Insufficient response to NSAIDs or local steroid injections • No data-driven definition of "active" disease, focus on quality of life	• Insufficient response to NSAIDs or local steroid injections • No data-driven definition of "active" disease, focus on quality of life

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index

Table IV - SIR (Società Italiana di Reumatologia, Italian Society for Rheumatology) recommendations for starting TNF inhibitors in patients with active psoriatic arthritis.

Peripheral arthritis	Axial disease	Enthesitis	Dactylitis
• Failure to NSAID therapy • Failure to at least two steroid injections (monoarthritis or oligoarthritis) • Failure to at least one of the DMARDs (MTX, CsA, SAS, LFN), administered alone or in combination for at least 3 months • At least one inflamed joint • VAS pain ≥40 (0-100 mm) • HAQ-DI ≥0.5 • Favourable expert opinion • New erosions or worsening of pre-existing • erosions on conventional x-rays	• Failure to at least 2 NSAIDs administered to maximal doses over a 3-month period • Favourable expert opinion • BASDAI ≥40 mm (0-100 mm)	• Failure over a 3-month period to NSAIDs therapy and to at least one DMARD as well as to at least 2 local steroid injections • Favourable expert opinion • VAS pain ≥40 (0-100 mm) • HAQ-DI ≥0.5 • Tenderness over inflamed entheses ≥2 on a 0-4 Likert scale	• Failure over a 3-month period to NSAIDs therapy and to at least one DMARD as well as to at least 2 local steroid injections • Favourable expert opinion • VAS pain ≥40 (0-100 mm) • HAQ-DI ≥0.5 • Tenderness over swollen digits ≥2 on a 0-4 Likert scale

MTX = methotrexate; CsA = cyclosporine; SAS = sulfasalazine; LFN = leflunomide; HAQ-DI = Health Assessment Questionnaire disability index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index.

PHARMACOECONOMIC ISSUES

TNFα blockers are very costly and not easily available to all patients, either relying on a national health system or on private insurance. However, illness costs in PsA were found high even without these drugs (47). In the Psoriatic Arthritis Cost Evaluation (PACE), an Italian cost-of-illness study on TNFα inhibitors in patients with PsA with a scarce response to traditional DMARDs, the cost per patient of PsA treatment for the society in the 6 months prior to the start of anti-TNFα therapy was € 1,519.17 (48). Anti-TNF-α agents, which are more expensive than conventional drugs, reduce disease activity and improve function and quality of life and are, therefore, able to reduce direct and indirect costs due to PsA. In last five-year period, some pharmacoeconomic studies addressed the question of whether anti-TNF-α therapy is cost-effective in PsA (48-52). A recent review evaluated the cost-effectiveness of etanercept, infliximab and adalimumab for the treatment of active PsA in patients who have an inadequate response to standard treatment (53). The study results suggest that etanercept would be considered the most cost-effective strategy for patients with PsA and minimal or mild-to-moderate psoriasis if the threshold for cost-effectiveness were £ 20,000-30,000 per quality-adjusted life year (QALY). All 3 biologics had a similar probability of being cost-effective for patients with PsA and moderate-to-severe psoriasis at a threshold of £ 20,000 per QALY.

In conclusion, all these studies have shown that anti-TNFα blocking agents are cost-effective on both the musculoskeletal and skin manifestations of psoriatic disease offering good value for money.

FUTURE PERSPECTIVES

As outlined above anti-TNFα agents represent a revolutionary innovation in the therapy of PsA. There is strong evidence that the currently available anti-TNFα agents all improve signs, symptoms, disability and quality of life and prevent radiological damage in PsA patients (12-15, 30, 31, 35, 36, 39-42).

The majority of studies have been performed in patients with polyarticular joint involvement. Therefore, data on the efficacy of these agents in other disease phenotypes such as those with dactylitis, enthesitis or predominant axial involvement are needed.

Because of a possible loss or lack of efficacy or intolerance to currently available TNFα antagonists, it would be highly desirable that the introduction of new drugs could add benefits in terms of efficacy, safety and more favourable routes or frequencies of administration. Newer biological therapies have been licensed for rheumatoid arthritis (rituximab, abatacept, tocilizumab) and for psoriasis (alefacept, ustekinumab). However, the role and benefits of these alternative non-anti-TNF biologics in PsA remain relatively unknown. Future biologics drugs for PsA could include new TNFα blockers, Interleukin 1, 6, 12, 23 and 17 inhibitors, co-stimulator modulator inhibitors, B cell depleting agents, small molecules and RANK/RANKL inhibitors (21).

With the growing number of treatment options, it is to be hoped that a therapeutical flow-chart is established. Therefore, there is an urgent need for head-to-head comparative trials assessing the added value of each new treatment compared with the existing ones.

CONCLUSIONS

Biologic drugs represent a revolutionary innovation in the therapy of PsA. Meta-analysis of randomised clinical trials showed that anti-TNF agents (infliximab, etanercept, adalimumab and golimumab) are more effective and equally safe compared with placebo in the management of PsA. Long-term observational studies have confirmed their effectiveness and safety profile.

Unlike traditional DMARDs, anti-TNF agents inhibit the progression of structural damage in peripheral joints. In addition, they are superior in reducing signs and symptoms of inflammation and in improving quality of life and functional status. Although anti-TNF-α agents are more expensive than conventional drugs, recent pharmacoeconomic studies have demonstrated their cost-effectiveness on both the musculoskeletal and skin manifestations of psoriatic disease.

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