Recommendations for the use of biologic therapy in the treatment of psoriatic arthritis: update from the Italian Society for Rheumatology

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ABSTRACT

Objective. *To update the 2006 Italian Society for Rheumatology recommendations for the use of biologic (TNF-α blocking) agents in the treatment of psoriatic arthritis (PsA).*

Methods. *A panel of experts performed a literature search and identified the items that required updating on the basis of new published data. A draft of the updated recommendations was circulated to a group of Italian Rheumatologists with a specific expertise in PsA and in therapy with biologic agents, and their suggestions were incorporated in the final version.*

Results. *A consensus was achieved regarding the initiation and the monitoring of anti-TNF-α agents in PsA. Inclusion and exclusion criteria were defined and specific recommendations were made for patients with psoriatic peripheral synovitis, spondylitis, enthesitis, and dactylitis, respectively. We also specified criteria for assessment of response to treatment and for withholding and withdrawal of therapy.*

Conclusions. *These recommendations may be used for guidance in deciding which patients with PsA should receive biologic therapy. Further updates of these recommendations may be published on the basis of the results of new clinical studies and of data from post-marketing surveillance.*

Background

Psoriatic arthritis (PsA) is a chronic inflammatory disorder typically characterised by arthritis and psoriasis variably associated with other extra-articular manifestations (1). A set of criteria (CASPAR, Classification criteria for psoriatic arthritis) has recently become available to classify PsA (2) (Table I). These criteria have been shown to have a 98.7% specificity and a 91.4% sensitivity in the original study, while their sensitivity in early PsA has been estimated to be in the range of 77.3–100% (3, 4).

PsA has traditionally been considered a milder and less disabling disease compared with rheumatoid arthritis (RA). However, in a population of PsA patients from a tertiary care Centre, where the gamut of disease expression is likely to be skewed toward the severe end of the spectrum, 40% of patients had joint erosions and damage (5, 6). In addition, about 20–40% of PsA patients have axial skeleton involvement ("psoriatic spondylitis") (7, 8), which may lead to functional limitation and deformity akin to, although usually less severe than that observed in ankylosing spondylitis (AS) (9). These and other (10) data suggest that a sizeable proportion of PsA patients have severe, potentially disabling disease requiring aggressive treatment, although the lack of population-based studies using standardised classification criteria precludes a confident estimate of the precise prevalence of severe PsA.

The initial treatment of PsA usually rests on non-steroidal anti-inflammatory drugs (NSAIDs) and topical steroid injections, but in patients with recalcitrant peripheral joint disease aggressive treatment with one or more disease-modifying anti-rheumatic agents (DMARDs) is indicated to suppress inflammation. In clinical practice, the most widely used DMARDs are methotrexate (level of evidence B), sulfasalazine (level of evidence A), leflunomide (level of evidence A), and cyclosporine (level of evidence B) (11-17). However, the efficacy of these agents in inhibiting articular erosions has not been assessed in proper controlled studies (12-17)

Table I. The Classification Criteria for Psoriatic Arthritis (CASPAR) Criteria.

To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with at least 3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis. Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.
   † A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider. A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.Evidence from at least one randomised controlled trial.
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.
3. A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.
5. Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

Reference: TAYLOR W, GLADMAN D, HELLIWELL P, MARCHESONI A, MEASE P, MIELANTS H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; 54: 2665-73.

(reviewed in (18)), and none of them has proved effective in ameliorating the symptoms of psoriatic spondylitis (11, 14, 18). In addition, the effectiveness of DMARDs in treating enthesitis and dactylitis is dubious.

There is strong evidence for a key role of the inflammatory cytokine TNF-α in the pathogenesis of PsA. In particular, *in situ* hybridisation studies have demonstrated the presence of TNF-α in psoriatic skin (19), in the synovium (20) of clinically involved joints and in inflamed entheses (21). Conversely, *ex vivo* studies have demonstrated significantly reduced serum levels of inflammatory mediators including interleukin-6, matrix metalloproteinases-2 and -9, vascular endothelial growth factor, and E-selectin following TNF-α blockade (22). Cell infiltration in affected skin and joints also appears to decrease after anti-TNF-α therapy (23). These findings have provided the rationale for using TNF-α inhibitors in PsA, but the proof of efficacy has actually been delivered by clinical data from randomised controlled trials (RCT) of TNF-α blockers in PsA (24) as well as from observational studies, including a large prospective study from the British Society for Rheumatology Biologics Register on 596 PsA patients (25). This latter study has also provided evidence that TNF-α inhibitors have a safety profile in PsA similar to that seen in patients with seronegative arthritis treated with DMARDs (25). Herein, we have reviewed the published evidence on the efficacy and safety of anti-TNF-agents in PsA, and proposed recommendations for their clinical use on the basis of the medical literature and of the opinions of Rheumatologists with an expertise in PsA and biological agents.

Epidemiology of psoriatic arthritis: disability and socio-economic impact

PsA is one of the commonest inflammatory arthropathies in Italy. An estimated 2-3% of the Italian population is affected by psoriasis, a third of which suffers from, or will eventually develop, PsA (26-28). Patients with PsA are prone to developing significant disability, and have reduced quality of life and increased mortality rates compared to the general population (29). This translates into high illness costs. An US study estimated the total cost for approximately 1.4 million patients with psoriasis or PsA to average $650 million in 1997 (30). However, since this estimate did not take into account indirect costs, which result from loss of resources (mainly productivity loss), the total economic burden related to PsA in the US is in all likelihood considerably greater. Another study based on the data from the national database of the German Collaborative Arthritis Centres estimated that direct and indirect costs related to PsA average €2,264 and €4,599 per patient/year, respectively (31).

Cost-effectiveness of TNF-α blockade in psoriatic arthritis

These guidelines are based on the principle "to maximise the health gain within the constraints of available resources and equity concerns" (32), in accordance with the approach followed by the National Institute of Clinical Excellence (NICE). The basis of NICE's cost-effectiveness analysis is the quality-adjusted life year (QALY), an index which combines the time a new treatment adds to a patient's lifespan with the quality of life that the patient experiences in that added time. Specifically, the cost-effectiveness of a new treatment compared with standard therapy is expressed as the ratio of the difference between the cost of a year's worth of treatment with the new drug and the cost of a year's worth of standard therapy over the difference between the new drug's and the standard therapy's QALY. This ratio is called the ICER, or incremental cost effectiveness ratio. The threshold for the ICER adopted by NICE to consider a treatment cost-effective is around £30,000 per year, which means that drugs exceeding this figure are unlikely to receive NICE approval. Based on these assumptions, a few pharmacoeconomic studies have addressed the question of whether anti-TNF-α therapy is indeed cost-effective in PsA.

Bansback *et al*. calculated the ICER of etanercept compared with DMARDs in PsA patients who had active disease and had failed two DMARDs (33). Using data from clinical trials and evidence- and expert opinion-based assumptions for disease progression, they calculated an ICER per QALY of £28,000 for the comparison against cyclosporine plus methotrexate and of £38,000 per QALY for the comparison with lefluno-

mide by 10 years. In their model, the ICER improved over time, consistent with a gain in QALYs related to delay in disease progression.

Another study, which used the Health Assessment Questionnaire to derive QALYs in PsA patients with active disease who had failed at least two DMARDs, estimated the ICER for etanercept compared with palliative care at 10 years at £26,361–£30,628, whereas the ICER for infliximab compared to palliative care within the same time frame was in the range of £165,363–£205,345 (34).

Olivieri *et al*. followed a different approach to assess cost-effectiveness of anti-TNF-α therapy in PsA (29). Instead of using published data to estimate the cost-effectiveness of anti-TNF-α *versus* conventional therapy, they enrolled and followed up for 12 months 107 clinical practice PsA patients with active disease who had failed or not tolerated conventional therapy. All patients were treated with TNF-α inhibitors (87% with etanercept) and evaluated with disease-specific and generic quality of life measures. Comparing the six-month pre-treatment period with the last six months of follow-up, they found an increase in drug-related costs that was only partially offset by the reduction in indirect costs, with a cost per QALY gained of €37,591 for social costs, €40,877 for the National Health System, and €40,943 for direct costs. The main point of this study was to demonstrate that anti-TNF-α therapy is cost-effective in the short-term clinical practice.

There are two points that are crucial to all pharmacoeconomic studies. The first is the calculation of QALYs, which requires some assumptions mainly related to the rate of disease progression with different interventions, the length of treatment, and the rebound scenarios after treatment withdrawal (34). The second point is the threshold value to be set for the ICER, which depends to some extent on the willingness of the healthcare payers to pay more to obtain additional QALYs (33). The results of the above studies suggest that etanercept may remain within the range of cost-effectiveness set by NICE. There is not enough data to judge the cost-effectiveness of other TNF-α blockers. From the clinical point of view, it is important to identify patients with active, DMARD-resistant PsA as treatment with biological agents would probably be most cost-effective in this subset of patients. In addition, recent data suggest that the absence of large-joint involvement and high C-reactive protein (CRP) levels independently predict a major clinical response to the TNF-α blocker infliximab (35). At the same time, it should be borne in mind that statistical models can not reliably predict clinical response in individual patients. Therefore, much of the effort should be focused on defining precise response criteria to biological agents within a given time frame, in order to avoid treating for long periods of time poorly or not responding patients. Finally, tentative advice should be given as to when treatment with biological agents may safely be withdrawn. All these points have been carefully considered in these recommendations.

Clinical trials on biological agents in psoriatic arthritis

Four anti-TNF-α compounds are licensed at the present in Italy for use in active, recalcitrant PsA. Etanercept (Enbrel®, Immunex Corporation [a wholly owned subsidiary of Amgen, Inc] Seattle, WA, US), a dimeric fusion protein consisting of the extracellular portion of the human p75 TNF- receptor linked to the Fc portion of a human IgG1, is administered subcutaneously at a dose of 25 mg twice weekly or of 50 mg once weekly. Infliximab (Remicade®, Centocor, Malvern, PA, US), a chimerical human-murine monoclonal anti-TNF-α IgG1 antibody, is administered intravenously at a dose of 5 mg/kg every 8 weeks. Adalimumab (Humira®, Abbott Laboratories, Abbott Park, IL, US) is a fully humanised monoclonal anti-TNF-α antibody, which is usually administered subcutaneously at a dose of 40 mg every other week.

Golimumab (Simponi®, Centocor Ortho Biotech Inc. and Schering-Plough Corporation, US), is a human monoclonal anti-TNF-α antibody given monthly as a 50 mg subcutaneous injection with or without methotrexate. Research is also pursuing the development of biological agents targeting molecules different from TNF-α.

A RCT has evaluated the efficacy and safety of the fusion protein of the first extracellular domains of human lymphocyte function-associated antigen 3 (LFA-3) and the Fc portion of IgG1 alefacept (Amevive®, Biogen Inc., Cambridge, MA, US) in combination with methotrexate *versus* placebo plus methotrexate. This study showed significant superiority of the combined therapy *versus* placebo and methotrexate (level of evidence A) (36).

Another RCT has demonstrated (level of evidence A) that ustekinumab (Stelara®, Janssen-Cilag International NV, Beerse, Belgium), a human monoclonal antibody that inhibits receptor-binding of the inflammatory cytokines interleukins 12 and 23, significantly reduced signs and symptoms of PsA and diminished psoriatic skin lesions compared with placebo (37). The efficacy of ustekinumab on psoriasis has been confirmed by a more recent RCT comparing ustekinumab with etanercept in patients with active psoriasis, which showed that ustekinumab given at a dose of 45 or 90 mg at week 0 and 4 was better than etanercept given at a dose of 50 mg twice weekly over 12 weeks (38). However, although approximately one fourth of patients in the three study arms had PsA, no formal analysis of the effect of ustekinumab on this manifestation was undertaken.

Finally, it has been reported (level of evidence C) that one patient with PsA resistant to TNF-α blockade responded to rituximab (39), while another patient with PsA resistant to DMARD therapy responded to abatacept (Orencia®, Bristol-Myers Squibb, Princeton, NJ, US) (40).

In this paper, we have mainly focused on the agents currently licensed in Italy for use in active PsA, but future updates of these recommendations will include any new agents that may be marketed in this country.

Etanercept

Etanercept (25 mg etanercept subcutaneously twice weekly) was evaluated

in a 12-week RCT *versus* placebo in 60 patients with PsA and psoriasis (41). All patients had active PsA (defined as 3 swollen joints and 3 tender or painful joints) at the time of study enrolment. The results of this study showed that 87% of etanercept-treated patients met the PsA response criteria (PsARC), compared with 23% of placebo-controlled patients. The American College of Rheumatology 20 response (ACR20) for joint improvement was achieved by 73% of etanercept-treated patients compared with 13% of placebo-treated patients. 26% of etanercept-treated patients achieved a 75% improvement in the psoriasis area severity index (PASI), compared with none of the placebo-treated patients. Etanercept was well tolerated and there were no withdrawals due to drug toxicity.

A subsequent 24-week RCT confirmed the efficacy and tolerability of etanercept treatment (25 mg subcutaneously twice weekly) in 205 patients with active PsA (42). At 12 weeks, 59% of etanercept patients met the ACR20 criteria compared with 15% of placebo patients, and these results were sustained at 48 weeks. Similarly, at 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least 75% improvement in the PASI compared with 3% of placebo patients. This study also assessed radiographic disease progression at 12 months using the modified total Sharp score. Etanercept, but not placebo, significantly inhibited radiographic progression (mean annualised rate of change in the modified total Sharp score -0.03 unit *versus* +1.00 unit in the placebo group). Overall, etanercept was well tolerated with adverse reactions occurring in similar numbers and intensities in both study arms. However, one etanercept-treated patient developed multiple sclerosis. In an open-label extension of this study, ACR20 criteria, PsARC, and PASI 50 criteria were met by 64%, 84%, and 62%, respectively, of etanercept-etanercept patients at the end of the 48-week open-label period (43). Placebo-etanercept patients achieved comparable results within 12 weeks that were sustained at 48 weeks (63%, 80%, and 73%). Radiographic progression was inhibited in the etanercept-etanercept patients (mean adjusted change in total Sharp score of -0.38 from baseline to 2 years). In placebo-etanercept patients, disease progression was inhibited after patients were started on etanercept (mean adjusted change of -0.22 from 1 year to 2 years). Adverse event rates were similar to those observed during the randomised phase.

The clinical efficacy and good tolerability of etanercept in PsA outlined in the above RCT have also been reported in a number of open studies and reports (44-47).

Infliximab

Numerous reports and open studies evaluating infliximab in active PsA have been published, but there are only two RCT (IMPACT [Infliximab Multinational Psoriatic Arthritis Controlled Trial] and IMPACT2). The first RCT, IMPACT involved 104 patients with active PsA (defined as affecting at least five active joints) who had failed at least one DMARD (48). Patients were randomised to receive infliximab at a dose of 5 mg/kg or placebo for 16 weeks. 65% patients in the infliximab group met the ACR20 response criteria, compared to only 10% in the placebo group. Similarly, among those treated with infliximab, 46% achieved ACR50 and 29% achieved ACR70 *versus* none of the placebo group. The average reduction of the PASI was 86% in the infliximab group compared to an average increase of 12% in the placebo group.

After week 16, patients initially randomised to placebo crossed over to receive infliximab 5 mg/kg every 8 weeks through week 50, while patients initially randomised to infliximab continued to receive active treatment at the same dose through week 50. Continued therapy with infliximab resulted in sustained improvement in articular and dermatologic manifestations of PsA through week 50. Mean changes from baseline to week 50 in the total modified van der Heijde score were -1.95 for the placebo-infliximab group and 1.52 for the infliximab-infliximab group (49). The incidence of adverse events was similar between the two treatment groups.

Seventy-eight of the 87 patients completing the first year of the IMPACT trial subsequently entered an open-label extension of the study (50). The results of the extension showed that at week 98 62%, 45% and 35% of the patients achieved ACR20, ACR50, and ACR70, respectively, while the percentages of patients with PASI improvement of at least 50%, 75% and 90% were 76%, 64% and 48%, respectively. No new safety issues emerged during the extension phase.

In the IMPACT2 trial, 200 PsA patients with active PsA and at least one plaque of psoriasis were randomised to receive infliximab 5 mg/kg or placebo (51). At week 24, patients initially randomised to placebo crossed over to receive infliximab 5 mg/kg every 8 weeks through week 54, while patients initially randomised to infliximab continued to receive active treatment at the same dose (or up to 10 mg/kg from week 38) through week 54. The proportion of patients achieving ACR20 response in the infliximab group was significantly greater than placebo at week 14 (58% and 11%, respectively) and at week 24 (54% and 16%, respectively). The proportion of patients with 3% body surface area at baseline achieving 75% improvement in PASI at week 14 was 63.9% and 2.3% in the infliximab and placebo groups, respectively ($p<0.001$). At week 14, 77% of infliximab patients achieved psoriatic arthritis response criteria (PsARC) compared with 27% of placebo patients ($p<0.001$). Dactylitis and enthesopathy improved significantly with infliximab compared with placebo. Arthritis and psoriasis responses were maintained through week 24. Infliximab-treated patients had significantly less radiographic damage compared to placebo-treated patients at week 24, and the inhibition of structural damage was sustained through week 54 (52). Of note, concomitant use of a synthetic DMARD (most commonly methotrexate) did not appear to have a significant effect on joint or skin response (53).

Infliximab was overall well tolerated in this study, with similar numbers of patients experiencing adverse events in each group, and in particular no deaths,

malignancies, cases of tuberculosis or other opportunistic infections were reported.

The results of the IMPACT and IMPACT2 studies are in agreement with numerous reports and open clinical trials (54-59), which have been reported more in detail in the previous version of these Recommendations (60).

Adalimumab

A RCT (Adalimumab Effectiveness in Psoriatic Arthritis Trial [ADEPT]) compared the efficacy and safety of adalimumab *versus* placebo in patients with active PsA and inadequate response to NSAIDs (61). Three hundred and fifteen patients were randomised to receive 40 mg adalimumab or placebo subcutaneously every other week for 24 weeks, and 140 patients in each study arm completed the trial. The primary efficacy end points were the ACR response rates, the quality of life, and the severity of skin disease in those patients with psoriasis involving at least 3% of body surface area. At week 24, 57%, 39% and 15% of the adalimumab-treated patients achieved respectively ACR20, ACR50 and ACR70 responses, compared with 15%, 6% and 1% of the placebo-treated patients. At the same time point, the mean change in the modified total Sharp score was -0.2 in patients receiving adalimumab *versus* 1.0 in those receiving placebo. Among the 69 adalimumab-treated patients evaluated with the PASI, 59% achieved a 75% PASI improvement response at 24 weeks, compared with 1% of the 69 placebo-treated patients evaluated. All the above differences were statistically significant. Disability and quality of life measures also significantly improved with adalimumab compared to placebo. Adalimumab was generally safe and well-tolerated, with a similar incidence of adverse reactions compared with that in the placebo group.

Two hundred and eighty-five of the completers of the ADEPT trial elected to enroll in an open-label extension of the study and received adalimumab 40 mg subcutaneously every other week for up to an additional 120 weeks (62). Compared with 24-week responses, inhibition of radiographic progression and improvements in joint disease were maintained in most patients during the open-label period. In particular, at week 104 57%, 45% and 30% of patients achieved ACR20, ACR50, and ACR70 responses, respectively, while the percentages of patients with no radiographic progression were 79% for the adalimumab-adalimumab group and 77% for the placebo-adalimumab group. Similarly, improvements in skin disease were maintained, with >20% of patients achieving the strict criterion of PASI 100 between week 48 and 104 of adalimumab treatment. The nature and frequency of adverse events during long-term adalimumab treatment were consistent with the safety profile during short-term treatment. These results thus show that adalimumab is effective in inducing clinical amelioration and in inhibiting radiographic progression in PsA during short-term treatment, and that these benefits are sustained during long-term treatment.

Another trial has been carried out to test the efficacy and safety of adalimumab in PsA (63). Differently from the ADEPT study, in this trial patients were required to have failed previous DMARD therapy, the treatment groups were of smaller size than in ADEPT, the double-blind period lasted 12 weeks only, and no radiographic assessment was included. Patients with active PsA were randomised to treatment for 12 weeks with subcutaneous adalimumab 40 mg every other week or placebo, followed by an open-label period with adalimumab. One hundred patients were enrolled (51 adalimumab, 49 placebo). At Week 12, ACR20, ACR50, and ACR70 responses were achieved by 39%, 25%, and 14% of adalimumab patients *versus* 16%, 2%, and 0% of placebo patients respectively, while a PsARC response was achieved by 51% of adalimumab *versus* 24% of placebo patients. These differences were statistically significant. At Week 12, measures of skin lesions and disability also significantly improved with adalimumab. After Week 12, open-label adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR20 response rates of 65% and 57%, respectively, observed at Week 24. Serious adverse events had similar frequencies during therapy with placebo (4.1%), blinded adalimumab (2.0%), and open-label adalimumab (3.1%). No serious infections occurred during adalimumab therapy.

Golimumab

There is a RCT which assessed the efficacy and safety of golimumab in patients with active PsA (64). Disease activity was defined by the presence of at least 3 swollen and 3 tender joints and active psoriasis. Patients were randomly assigned to receive subcutaneous injections of placebo (n=113), golimumab 50 mg (n=146), or golimumab 100 mg (n=146) every 4 weeks through week 20. Outcome measures included the ACR response criteria, the PASI in patients in whom at least 3% of the body surface area was affected by psoriasis at baseline, the modified Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) index for enthesitis (65) and disease-specific and generic quality of life questionnaires. At week 14, 51% of patients receiving golimumab 50 mg, and 45% of patients receiving golimumab 100 mg achieved an ACR20 response compared with 9% of patients receiving placebo. Similarly, significantly more golimumab-treated patients attained ACR50 and ACR70 responses. Among the 74% of patients in whom at least 3% of the body surface area was affected by psoriasis at baseline, 40% of those in the golimumab 50 mg group and 58% of those in the golimumab 100 mg group had at least 75% improvement in the PASI at week 14 compared with 3% of placebo-treated patients. Significant improvement was also observed for the PsA-modified MASES index and for quality of life measures with golimumab compared to placebo. This efficacy was maintained through week 24. Golimumab was generally well tolerated.

Alefacept

A RCT has evaluated the efficacy and safety of the fusion protein of the first extracellular domains of human lymphocyte function-associated antigen

3 (LFA-3) and the Fc portion of IgG1 alefacept in combination with methotrexate *versus* placebo plus methotrexate (36). Prerequisite for study entry was active PsA defined as at least three tender and swollen joints despite treatment with methotrexate for at least three months at a stable dose for a minimum of four weeks. Alefacept (15 mg) or placebo was administered intramuscularly once weekly for 12 weeks in combination with methotrexate, followed by 12 weeks of observation during which only methotrexate was continued. The primary efficacy end point was the proportion of patients achieving an ACR20 response at week 24. One hundred eighty-five patients were randomly assigned to receive alefacept plus methotrexate (n=123) or placebo plus methotrexate (n=62). At week 24, 54% of patients in the alefacept plus methotrexate group achieved an ACR20 response, compared with 23% of patients in the placebo plus methotrexate group. The proportion of patients achieving ACR50 and ACR70 responses were 17% and 7% for the alefacept plus methotrexate arm *versus* 10% and 2% for the placebo plus methotrexate arm. In the 87 patients with psoriasis involving at least 3% of the body surface area, a 50% reduction from the baseline PASI at week 14 was achieved by 53% of patients receiving alefacept plus methotrexate compared with 17% of those receiving placebo plus methotrexate. All these differences were statistically significant except for those related to the ACR50 and ACR70 responses between the two study groups.

Most adverse events were mild to moderate in severity. In the alefacept plus methotrexate group, the incidence of serious adverse events was low (1.6%), and no opportunistic infections or malignancies were reported. These results thus demonstrate that alefacept in combination with methotrexate is an effective and safe treatment for PsA.

Ustekinumab

Ustekinumab is a novel human monoclonal antibody that inhibits receptor-binding of the inflammatory cytokines interleukins 12 and 23. Ustekinumab is licensed in Italy for use in refractory, moderate to severe psoriasis, but there is evidence that it may also be effective in ameliorating joint disease in PsA. A RCT has compared the efficacy and safety of subcutaneous ustekinumab (90 mg or 63 mg) every week for 4 weeks (weeks 0–3) followed by placebo at weeks 12 and 16 (n=76; Group 1) or placebo (weeks 0–3) and ustekinumab (63 mg) at weeks 12 and 16 (n=70; Group 2) (37). The first 12 weeks of the study were placebo-controlled. Masking was maintained to week 16, and patients were followed up to week 36. The primary endpoint was ACR20 response at week 12. Efficacy analyses were performed on the intention-to-treat population. At week 12, 42% patients in Group 1 and 14% in Group 2 achieved the ACR20 criteria. ACR50 and ACR70 response rates at week 12 were 25% and 11% for group 1 and 7% and 0% for group 2, respectively. Of 124 (85%) participants with psoriasis affecting 3% or more body surface area, 52% in group 1 and 5% in group 2 had an at least 75% improvement in PASI score at week 12. During the placebo-controlled period (weeks 0-12), adverse events were recorded in 61% of patients in group 1 and 63% in group 2, while serious adverse events were recorded in 4% of group 2 patients only. This data suggest a role for ustekinumab in the treatment of active PsA, although larger and longer trials are needed to better define the efficacy and safety profile of ustekinumab.

Guidelines for the clinical use of anti-TNF-α agents in psoriatic arthritis: rationale and goals

In view of the above considerations, the Italian Society for Rheumatology (SIR, Società Italiana di Reumatologia) has deemed it appropriate to set up a special interest group to develop specific guidelines for the use of anti-TNF-α therapies in patients with PsA.

The following points have been considered in developing these guidelines:

– the use of anti-TNF-α agents in active PsA patients resistant or intolerant to conventional DMARDs appears justified in the light of the clinical studies published so far, which have unequivocally demonstrated the effectiveness of TNF-α blockade in peripheral joint synovitis in PsA (level of evidence 1a, strength of recommendation A);

– anti-TNF- agents have proved effective in AS, a condition similar to psoriatic spondylitis (level of evidence 1a, strength of recommendation A);

– since anti-TNF-α therapy is costly and PsA has an elevated prevalence in the Italian population, it is crucial to identify those patients that can benefit most from anti-TNF-α therapy;

– response to treatment should be adequately monitored by appropriate response criteria, and non-responders should discontinue anti-TNF-α therapy;

– the potential long-term effects of TNF-α blockers are still unknown, but their safety profile appears so far to be good.

The objective of these guidelines is to provide guidance in the use of biological agents to clinicians caring for PsA patients who are entitled to use them.

More specifically, our goals are:

– To improve the clinical symptoms and signs of patients with PsA not responsive to NSAIDs or conventional DMARDs;

– To ensure that patients that have the most to gain from anti-TNF-α therapy receive this treatment;

– To guarantee that use of anti-TNF-agents be undertaken only by experienced Rheumatologists in specialised Centres;

– To avoid improper use of these agents that could lead to patients' harm and economic burden on the society;

– To monitor both clinical response and adverse events by common parameters across different Centres;

– To make it possible in the future to assess the benefits for the patients and the cost implications using the following parameters:

- Prevention of disability;
- Decreased rate of hospital admissions;
- Decreased need for rehabilitative interventions;
- Prevention of, or reduced need for, orthopedic surgery;
- Reduced intake of other medications (NSAIDs, analgesic);
- Reduced use of social services;

- Reduced need for domestic aid;
- Preservation and improvement of quality of life and of life expectancy.

Choice of the TNF-α antagonist

In PsA, no specific TNF-α inhibitor has been demonstrated to be more effective than others (24). Therefore, we feel that drug choice should be made taking into account the patient's preferences as well as the available safety data and patient's co-morbidities (66). Patients with associated inflammatory bowel disease should be treated with the monoclonal antibodies infliximab or adalimumab, whereas patients at risk of tuberculosis (TB) should preferentially receive etanercept, which has the lowest risk of inducing TB among TNF-α blockers (67) (level of evidence 2b, strength of recommendation B). Finally, because uveitis has been shown to occur significantly more often during etanercept than during infliximab and adalimumab treatment, we suggest that patients with PsA and uveitis be preferentially treated with a monoclonal antibody (68) (level of evidence 2b, strength of recommendation B).

Therapeutic regimens of TNF-α inhibitors

As a rule, patients should be treated according to the dose and frequency of administration specified for each TNF-α inhibitor. It has been proposed (69, 70) that some patients whose disease is in remission on anti-TNF-α therapy may be able to remain in remission with a reduced dose, or a reduced frequency of treatment (reviewed in (71)). However, this issue remains a matter of debate, as the evidence accrued so far in the treatment of the spondyloarthropathies is controversial (69, 72, 73). We feel that, in patients whose disease is in remission, treatment with TNF-α inhibitors with a reduced dose, or a reduced frequency may be attempted if the patients have been long enough in remission (see the "Withdrawal of anti-TNF-α therapy due to disease remission" section below) (level of evidence 5, strength of recommendation D). In patients who respond partially to infliximab, the frequency of administration may be increased up to every six weeks (66) (level of evidence 4, strength of recommendation C). In contrast, a RCT (reported so far only in abstract form) comparing two different regimens of etanercept (50 mg twice weekly *versus* 50 mg once weekly) showed that although the higher-dose regimen was more effective in treating skin manifestations, the two regimens were of comparable efficacy for joint disease (ACR20, ACR50 and ACR70 met at week 12 by 66%, 45% and 20% of patients treated with the higher dose compared with 61%, 41%, and 22% of patients on standard dosage, respectively) (74) (level of evidence 1b, strength of recommendation A).

Inclusion criteria

To be eligible for treatment with anti-TNF-α agents, patients should have active PsA. PsA should be diagnosed according to the CASPAR criteria (2), but may also be diagnosed by a Rheumatologist with an expertise in PsA when the CASPAR criteria are not met if the clinical manifestations are strongly suggestive and other types of arthritis are excluded. Psoriasis should preferably be diagnosed by a Dermatologists (75). Traditionally, PsA is stratified in 5 clinical subgroups according to the Moll and Wright criteria (76). However, this classification does not include subsets of PsA that are now well recognised, such as psoriatic enthesitis and dactylitis (77). Equally important, there is evidence from longitudinal studies that these subsets do not always remain distinct over time but that may evolve from one form into another (78). In fact, only two of the subgroups identified by Moll and Wright appear to be really distinct, psoriatic spondylitis (with or without peripheral arthritis) and PsA with peripheral involvement in the absence of axial disease (79). These two subgroups are characterised by different response to therapy, because there is no evidence that psoriatic spondylitis responds to treatment with DMARDs.

For therapeutic purposes, we elected to stratify PsA depending on the predominant involvement as a) PsA with peripheral arthritis, b) psoriatic spondylitis, c) PsA mainly characterised by enthesitis and d) PsA mainly characterised by dactylitis.

a) *PsA with peripheral arthritis*

Anti-TNF-α therapy should be considered in patients with PsA predominantly characterised by peripheral synovitis if:

– They have not responded to NSAID therapy and to at least one of the DMARDs most commonly used in PsA (methotrexate, cyclosporine, sulfasalazine, leflunomide), administered alone or in combination for at least three months (for two months at full therapeutic or tolerated doses unless contraindicated). We consider "full therapeutic doses" 2–3 grams per day for sulfasalazine, 20 mg per week for methotrexate, 3–5 mg per kg/body weight per day for cyclosporine, and 20 mg per day for leflunomide. Patients with monoarthritis or oligoarthritis should also have failed at least two steroid injections.

plus

– Have at least one inflamed joint. A joint is considered inflamed if it is tender and painful, with pain not relieved by rest, as well as swollen (excluding "bony" swelling only, which may be due to structural damage in the absence of active synovitis).

– VAS pain ≥40 on a 100 mm scale and HAQ-DI (Health Assessment Questionnaire – disability index) ≥0.5.

– Favourable Expert Opinion (as defined in "Assessment of response to, and criteria for withdrawal of anti-TNF-α therapy" below).

Patients may also be considered for anti-TNF-α therapy if they develop new erosions or worsening of pre-existing erosions consistent with PsA on conventional x-rays, even if they have an acceptable clinical response to their treatments.

b) *Psoriatic spondylitis*

Anti-TNF-α therapy should be considered in patients with PsA characterised predominantly by axial involvement (sacro-iliitis and/or spondylitis) in agreement with the Recommendations recently proposed by the International ASAS (Assessment of SpondyloArthritis International Society) working group (80) if:

– They have not responded over a 3-month period to maximal doses of at least 2 NSAIDs

plus

fulfill the following 2 criteria:
– Favourable Expert Opinion;
– Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥40 mm (VAS 0–100 mm)

c) *PsA characterised by enthesitis*
Anti-TNF-α therapy should be considered in patients with PsA characterised predominantly by peripheral enthesitis if:
– They have not responded over a 3-month period to NSAIDs therapy and to at least one DMARD as well as to local steroid therapy (at least 2 steroid injections).
– Favourable Expert Opinion.

plus

fulfill the following 2 criteria:
– VAS pain ≥40 on a 100 mm scale and HAQ-DI ≥0.5.
– Tenderness over-inflamed entheses ≥2 on a 0–4 Likert scale.

d) *PsA characterised by dactylitis*
Anti-TNF-α therapy should be considered in patients with PsA characterised predominantly by dactylitis if:
– They have not responded over a 3-month period to NSAIDs therapy and to at least one DMARD as well as to local steroid therapy (at least 2 steroid injections).
– Favourable Expert Opinion.

plus

fulfill the following 2 criteria:
– VAS pain ≥40 on a 100 mm scale and HAQ-DI ≥0.5.
– Have uniformly swollen digit(s) and tenderness over swollen digits ≥2 on a 0–4 Likert scale.

Exclusion criteria
We recommend that only licensed agents be used and that the indications reported in the drug information leaflets be carefully adhered to, particularly in patients that are at risk of infections. Since the safety of anti-TNF-α agents has not been established in pregnant or lactating patients (81), these agents should not be administered during pregnancy and lactation (level of evidence 4, strength of recommendation C). Patients who become pregnant during treatment should discontinue anti-TNF-α agents as a matter of precaution. However, female patients in fertile age are not required to take pregnancy tests prior to commencing biologic treatment (66, 82).
There is no evidence that TNF-α inhibitors impair fertility in females, while it is not established whether or not they do so in males (83). Male patients should be informed accordingly before being commenced on TNF-α blockers, and sperm samples stored in a sperm bank if they wish.
In addition, anti-TNF-α agents are contraindicated in the following conditions:
– known hypersensitivity to a specific anti-TNF-α agent (an agent different from that responsible for inducing hypersensitivity may be used);
– sepsis or high risk of developing sepsis;
– active infections including TB, hepatitis B virus (HBV), human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS);
– previous TB not adequately treated;
– neoplasms over the last 5 years (except for basal cell carcinoma), in agreement with the French recommendation for the biological treatment of PsA (66);
– heart failure class III or IV according to the New York Heart Association (NYHA);
– demyelinating disorders.
In addition, since the risk of developing non-melanoma skin cancer is increased in psoriatic patients treated with more than 1000 joules cumulative dosage of PUVA, if these patients receive TNF-α agents they should be reviewed yearly by a Dermatologist as a matter of precaution (84, 85).
There is now limited evidence suggesting that TNF-α inhibitors may carefully be used in selected patients with severe PsA and HIV infection, provided that CD4 count is >200 per mm^3, that HIV viral load is <60,000 copies per mm^3, and that immunologic and viral parameters are closely monitored under guidance of an Infective disease Specialist (86, 87). Therefore, in agreement with the guidelines by the British Society for Rheumatology (82), we do not consider chronic HIV infection an absolute contraindication to TNF-α blocker therapy, although these therapies should be considered only as a "last resort" and strict surveillance by a Specialist in Infectious Diseases of HIV patients receiving TNF-α inhibitors is required (level of evidence 4, strength of recommendation C).
The evidence regarding biological treatment of patients affected by chronic HBV infection is also limited. In seven reported cases (four with Crohn's disease and three with arthritis), infliximab therapy resulted in increased activity of HBV infection, hepatitis, or both in five cases (86). Of the two patients that did not flare, one received lamivudine prophylaxis, while of the five that flared four received lamivudine treatment. Three of the four lamivudine-treated patients had a favourable outcome, and one only required a liver transplant. Reactivation time from last infliximab infusion ranged from 10 days to 3 months. The mechanism by which TNF-α inhibition leads to HBV reactivation has been hypothesized to involve increased expression of viral antigens followed by the development of an immunemediated injury after the inhibitory effects of anti-TNF-α therapy wane (86). It is unclear which is the best scheme to prevent HBV reactivation in patients undergoing anti-TNF-α therapy. One option would be to treat all patients prophylactically with lamivudine, although this preventative intervention has the potential risk of inducing resistance. The other option would be to closely monitor patients for evidence of liver injury. The main concern with this approach is that flares of HBV infection may occur quite rapidly, thus causing liver damage before antiviral therapy is commenced. We feel that anti-TNF-α therapy should be used only if absolutely required after failure of safer treatments, and that patients with chronic HBV infection

receiving this therapy should be placed under strict surveillance by a Specialist in Infectious Diseases. Finally, HBV-negative subjects at high risk for HBV infection should be counseled about the opportunity to be vaccinated against HBV before starting biological treatment.

Monitoring of disease activity

It has previously been demonstrated that active joint count can reliably assess disease activity in PsA characterised by predominant peripheral joint involvement (88). The most widely used measure of drug efficacy in clinical trials is the ACR response criteria, which are also part of the core set of domains for PsA assessment established at OMERACT 8 (89). In particular, a 68 tender and a 66 swollen joint count is recommended in PsA. Thus, we elected to use the ACR response criteria for evaluation of peripheral arthritis in PsA.

Psoriatic spondylitis should be assessed using the outcome variables outlined in the International ASAS consensus statement for the use of anti-TNF- agents in AS (90), which have been shown to perform well when applied to PsA patients with axial disease (91). We elected to score enthesitis for the purpose of clinical assessment using the MASES, an index validated in PsA patients (92), which includes thirteen common sites of entheseal involvement (65).

We recommend that dactylitis be assessed by counting the digits involved and by evaluating the degree of tenderness of each digit involved. The assessment of dactylitis based on the number of digits involved and the degree of tenderness has been shown to be sensitive to change in clinical trials with infliximab (48, 51).

In order to comprehensively assess the response to anti-TNF-α therapy, we recommend that disease activity be monitored using the following parameters whenever appropriate (89, 91-95):

- Tender joint count.
- Swollen joint count.
- Pain on VAS scale.
- Patient's global assessment of disease activity.
- Physical function (Health Assessment Questionnaire.
- Health Assessment Questionnaire Disability Index (HAQ-DI).
- MASES (Maastricht Ankylosing Spondylitis Enthesis Score) (for patients with enthesitis).
- Count of digits with dactylitis.
- Assessment of dactylitis' tenderness using a 0–3 VAS (0: absence of tenderness, 1: tenderness, 2: tenderness with wincing, 3: tenderness with wincing and withdrawal).
- BASDAI (for patients with spinal involvement).
- Indices of spinal mobility (Schober's test, spinal lateral flexion, chest expansion, cervical spine flexion, and tragus-to-wall distance) (for patients with spinal involvement).
- Expert Opinion.

Although no specific monitoring for blood toxicity is required, we recommend that in patients receiving anti-TNF-α agents the complete blood count, liver function tests, and ANA be checked at baseline and at 3–6-monthly intervals as a matter of precaution. If a DMARD is co-prescribed, then monitoring should be performed according to the guidelines for the relevant DMARD (96).

Assessment of response to, and criteria for withdrawal of anti-TNF-α therapy

Response to anti-TNF-α therapy should be assessed 3 months after treatment onset. Expert (the treating Rheumatologist's) opinion should be based on evaluation of clinical symptoms and signs, of laboratory investigations (particularly acute phase reactants), and of imaging studies whenever appropriate.

Assessment of treatment efficacy

For anti-TNF-α therapy to be considered effective, the following criteria should be satisfied:

a) *PsA with peripheral arthritis*

– in patients with psoriatic polyarthritis (5 affected joints), ≥50% reduction in the number of tender and swollen joints and 50% improvement of at least 3 of the remaining ACR50 criteria.

– in patients with DMARD-resistant mono- or oligoarthritis ≥50% decrease in VAS pain compared to baseline.

– Expert opinion that anti-TNF-α therapy should be continued.

b) *Psoriatic spondylitis*

– ≥50% relative or ≥two-point absolute im-provement in the BASDAI score assessed on an numerical rating scale (equivalent to 20 mm on a 100 mm VAS).

– Expert opinion that anti-TNF-α therapy should be continued.

c) *PsA characterised by enthesitis*

– ≥50% decrease in VAS pain compared to baseline.

– ≥20% reduction in the MASES in patients with ≥3 clinically inflamed entheses at baseline and

– Expert opinion that anti-TNF-α therapy should be continued.

d) *PsA characterised by dactylitis*

– ≥50% decrease in VAS pain compared to baseline;

– in patients with ≥5 digits involved at baseline, dactylitis (*i.e.* digit swelling and tenderness) should resolve in at least 20% of involved digits;

– Expert opinion that anti-TNF-α therapy should be continued.

Patients who meet the criteria at three months should be clinically re-assessed at six months and subsequently on a yearly basis using the outcome measures reported above as long as they are on biologic therapy.

Patients who, at three months, do not meet the above response criteria, should be considered treatment failures. However, if in the Expert's opinion at least a partial, significant clinical improvement has occurred within the first 3 months (for instance, resulting in a reduction in the NSAID dose), treatment may be continued for a further three months, and patients reassessed after that period of time.

Management of patients who fail one biological agent

There is limited data on switching from one TNF-α inhibitor to another in PsA. An observational Italian study showed that in ten PsA patients who switched from infliximab to etanercept the proportion of PsARC responders increased

from 10% to 70%, while in seven patients who switched from etanercept to adalimumab the proportion rose from 14% to 57% (97). Two other PsA patients who successfully switched from infliximab to etanercept and a patient with severe HLA-B27-associated heel enthesitis who successfully switched from adalimumab to etanercept have been described in France (98) and Italy (99), respectively. Finally, preliminary data (reported in abstract form) have shown that 12 weeks after switching to adalimumab from another TNF-α inhibitor, 67%, 42%, and 25% of 66 PsA patients met the ACR20, ACR50, and ACR70 response criteria, respectively (74).

On the basis of these observations and in agreement with other guidelines (82) and recommendations (66), we recommend that PsA patients who fail a TNF-α inhibitor be given the option of trying another TNF-α inhibitor and reassessed after three months (level of evidence 4, strength of recommendation C). 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 that has failed (*i.e.* a monoclonal antibody in patients that had received the receptor and the other way round). However, this recommendation is based on Expert opinion rather than on evidence (level of evidence 5, strength of recommendation D).

In patients who fail TNF-α inhibitors, these drugs must be withdrawn, although other biologic agents may be considered on a named basis.

Patients who meet the clinical response criteria but develop new erosions or worsening of pre-existing erosions on conventional x-rays may be considered for treatment with another biological agent or for co-treatment with a DMARD, although evidence from clinical trials is lacking that concomitant DMARD administration increases the efficacy of anti-TNF-α therapy (66) (level of evidence 5, strength of recommendation D).

Data from a Swedish register showed combined methotrexate therapy with etanercept, infliximab or adalimumab to be associated with long-term anti-TNF-α survival in PsA patients (100). However, this effect of methotrexate appeared to be primarily due to a decreased frequency of drop-outs. This reported effect of methotrexate has not been confirmed by an analysis of a cohort of PsA patients receiving etanercept with and without concomitant methotrexate, in which methotrexate use did not predict anti-TNF-α survival (101).

Discontinuation of anti-TNF-α therapy

Withdrawal of anti-TNF-α therapy due to lack of efficacy

Anti-TNF-α therapy should be discontinued if patients do not meet the response criteria outlined above in the "Assessment of response to, and criteria for withdrawal of anti-TNF-α therapy" section despite having tried two TNF-α inhibitors (three if at least one TNF-α inhibitor was withdrawn due to toxicity or intolerance).

Withdrawal of anti-TNF-α therapy due to drug toxicity

Anti-TNF-α therapy should be discontinued at any time if any of the following event occurs:

– any serious adverse event judged to be drug-related, including lupus-like syndrome (102), leukocytoclastic vasculitis (102), demyelinating disease (103), uveitis (68, 104), interstitial lung disease (102), and severe worsening of psoriasis (105);

– development of neoplasm;

– development of serious intercurrent infection (withdrawal may be temporary)

– pregnancy (withdrawal may be temporary);

– major surgical procedures: we feel that as a matter of precaution anti-TNF-α agents should be withheld for at least three half lives preoperatively and restarted a couple of weeks when wound healing has set in, in agreement with the suggestions by a recent review article (106).

Withdrawal of anti-TNF-α therapy due to disease remission

Theoretically, remission of PsA could justify the withdrawal of ongoing anti-TNF-α therapy. Recent evidence in favour of this approach in PsA characterised by peripheral synovitis has been provided by an Italian prospective, case-control study that demonstrated that remission occurred in up to 24% of patients with peripheral PsA (107). Remission was significantly more frequent, although not longer, in patients receiving anti-TNF-α drugs compared to DMARDs. This study also provided evidence that PsA patients could remain in remission for prolonged time after therapy discontinuation.

There is no direct evidence on the outcome of patients with PsA spondylitis who have entered remission with TNF-α inhibitors after treatment withdrawal. However, a study showed that nearly all (97.6%) patients with AS (a condition similar to PsA spondylitis) in remission flared after withdrawal of anti-TNF-α therapy (108).

Likewise, there is no data on the outcome of patients with PsA enthesitis who have entered remission with TNF-α inhibitors after treatment withdrawal. Indirect evidence is derived from a case of HLA-B27-associated enthesitis that went into remission with etanercept and had no flare after drug withdrawal (99). Similarly, in a population of ankylosing spondylitis patients, enthesitis assessed at MASES sites resolved in about 50% of affected subjects following treatment with adalimumab for 12 weeks (109).

There is no data on the outcome of patients with PsA dactylitis who have entered remission with TNF-α inhibitors after treatment withdrawal.

Although there are no commonly accepted criteria to define remission in PsA (110), it has been proposed (107) that PsA may be considered as being in remission if the following criteria are satisfied : fatigue (VAS 1–100mm) <10, pain (VAS 1–100mm) <10, articular morning stiffness <15 minutes, active (tender and swollen) joint count 0, normal ESR and CRP values, and absence of dactylitis, enthesitis, tenosynovitis, inflammatory spinal pain, and extra-articular manifestations. "Bony" swelling only, which is due to structural damage, should not be considered a sign of active joint disease. Likewise, uniform digit swelling in the absence of pain and tenderness is a characteristic of chronic dactylitis (111), which again should not

be considered a sign of active PsA.
If a patient with PsA is in remission, withdrawal may be considered in the following instances:

a) *PsA with peripheral arthritis*
If the above criteria are met and the patient has been in clinical remission without evidence of radiographic progression for at least one year.

b) *Psoriatic spondylitis*
Treatment withdrawal is not recommended in this subset, since there is evidence that nearly all patients with AS (a condition similar to PsA spondylitis) flare upon discontinuation of TNF-α inhibitors as outlined above.

c) *PsA characterised by enthesitis*
If the above criteria are met and the patient has been in clinical remission for at least six months.

d) *PsA characterised by dactylitis*
If the above criteria are met and the patient has been in clinical remission for at least four months.

Treatment Centres and Expert Opinion
Anti-TNF-α therapy is complex in that it requires a specific expertise in diagnosis, assessment of disease activity, drug administration, therapeutic monitoring, and management of adverse reactions. Therefore, we recommend that use of TNF-α blockers be undertaken only by experienced Rheumatologists in selected specialised Centres, namely University Clinics and Rheumatology Units in Hospitals.

Updates of the Recommendations
The Italian Society for Rheumatology will implement further updates of these Recommendations on the basis of the results of new clinical studies and of data from post-marketing surveillance (112). Any of the statements made herein may be modified on the basis of new clinical and pharmacoeconomic data and long-term safety considerations.

Methods
Research of published studies
We searched Medline (2006 through March 2010) using the key words "psoriatic arthritis", "infliximab", "etanercept", "adalimumab", "golimumab", and "tumour necrosis factor (subheading: antagonists and inhibitors)". We also made combined searches of other biological agents currently used to treat RA and PsA in order to capture studies done with biological agents other than TNF-α inhibitors. Finally, we reviewed relevant abstracts of the annual meetings of the ACR as well as abstracts of the European League against Rheumatism (EULAR) from 2006 to 2009. The retrieved papers were included in our analysis if they were pertinent to the diseases and treatments considered, if they were in English, if the diagnosis was reliably established, and if sufficient information could be extracted with regard to treatment. Editorials, review articles, authors' replies and broadly speaking manuscripts not reporting treatment of patients have not been considered for analysis. Evidence of grade 2 or lower has been considered whenever evidence of grade 1 was unavailable.
Levels of evidence have been assigned to the papers retrieved, and the strength of the recommendations has been graded according to the levels of evidence

Grading of the evidence
We used the levels of evidence outlined by the Centre for Evidence-based medicine (113):
1a Systematic Review (SR) (with homogeneity) of RCTs.
1b Individual RCT (with narrow Confidence Interval).
1c All or none.
2a SR (with homogeneity) of cohort studies.
2b Individual cohort study (including low quality RCT; *e.g.* <80% follow up).
2c Ecological studies.
3a SR (with homogeneity) of case-control studies.
3b Individual case-control study.
4 Case-series (and poor quality cohort and and case-control studies).
5 Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".

Grades of recommendations
A Consistent with level 1 studies.
B Consistent level 2 or 3 studies or extrapolations from level 1 studies.
C Level 4 studies or extrapolations from level 2 or 3 studies.
D Level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

Consensus methodology
Recommendations were generated by three panel members on the basis of the evidence extracted by the literature. In a modified nominal group technique, all group members were subsequently engaged in round-robin feedback sessions until full consensus was achieved.

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