Recommendations of the Italian Society for Rheumatology for the use of biologic (TNF-α blocking) agents in the treatment of psoriatic arthritis

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Abstract

Aim

To propose recommendations for the use of biologic (TNF-α blocking) agents in the treatment of psoriatic arthritis (PsA).

Methods

We developed these recommendations by reviewing the evidence published in medical journals and in abstracts of the American College of Rheumatology (ACR) and of the European League against Rheumatism. A draft of the recommendations was circulated to a group of Italian Rheumatologists with a special interest 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. More specifically, we propose that anti-TNF-α agents be considered in active PsA resistant to non-steroidal anti-inflammatory drugs, to at least two local steroid injections and at least 2 conventional disease-modifying anti-rheumatic agents (in cases of oligo/monoarthritis and/or enthesitis), and to at least two conventional disease-modifying anti-rheumatic agents (in patients with peripheral joints synovitis). Disease activity monitoring should be based on a variety of outcome measures including the ACR response criteria modified for use in PsA, the Bath ankylosing spondylitis disease activity index (BASDAI), and the Maastricht ankylosing spondylitis enthesis score (MASES). A favorable Expert opinion, based on evaluation of clinical symptoms and signs, of laboratory investigations (particularly acute phase reactants), and of imaging studies (whenever appropriate) should also be obtained.

Conclusions

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

Key words

Psoriatic arthritis, TNF-α blocking, recommendations, Italian Society for Rheumatology.

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Background

Psoriatic arthritis (PsA) is a chronic inflammatory disorder characterized by arthritis and psoriasis variably associated with other extra-articular manifestations (1). PsA is usually grouped among the seronegative spondyloarthropathies (SpA), a class of diseases encompassing ankylosing spondylitis (AS) and reactive arthritis, with which it shares a number of common immunogenetical, radiological, and clinical features (2). Research studies have provided evidence that the inflammatory cytokine TNF-α plays a key role in the pathogenesis of the SpA, including PsA. In particular, *in situ* hybridization studies have demonstrated the presence of TNF-α in psoriatic skin (3), in the synovium (4) of clinically involved joints and in inflamed entheses (5). Thus, therapies targeting TNF-α may be potentially useful in controlling disease activity in PsA.

PsA has traditionally been considered a milder and less disabling disease compared with rheumatoid arthritis (RA). However, this view has recently been challenged by a number of studies showing that approximately 40% of PsA patients develop joint erosions and damage (6, 7). In addition, in circa 20-40% of patients, PsA can also affect the axial skeleton (so-called "psoriatic spondylitis") (8), leading to functional limitation and deformity akin to, although usually less severe than that observed in AS (9) .

The initial treatment of PsA is usually based on non-steroidal anti-inflammatory drugs (NSAIDs) and topical steroid injections. However, in patients with active joint disease not responsive to NSAIDs, 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), and ciclosporin (level of evidence B), but their efficacy in inhibiting articular erosions has not been assessed in proper controlled studies (10-15) (reviewed in (16)). Even if there is level of evidence A for clinical efficacy of sulfasalazine in the treatment of peripheral synovitis in PsA, the entity of the benefit conferred is quite limited (11). In addition, none of these agents has proved effective in ameliorating the symptoms of psoriatic spondylitis, including pain and early morning stiffness (12). Leflunomide has recently been shown in a randomized controlled trial (RCT) to be effective in the treatment of psoriasis and PsA (level of evidence A) (17), but no data on its action on radiographic progression has been presented.

Recently, a new class of drugs that share the common mechanism of blocking TNF-α (anti-TNF-α agents) has been shown to inhibit joint erosions in RA. Anti-TNF-α agents have been investigated less extensively in the SpA including AS and PsA than in RA, but a number of research and clinical studies suggest that they may also be beneficial in AS (18, 19) and in recalcitrant PsA (20-22). Herein, we review the evidence supporting the role of anti-TNF-α agents in PsA and propose some preliminary guidelines for their clinical use.

Epidemiology of psoriatic arthritis: disability and socio-economic impact

PsA is one of the commonest inflammatory arthropathies in Italy. It is estimated that 2-3% of the Italian population is affected by psoriasis, a third of which suffers from, or will eventually develop, PsA (23-25). Recent reports suggest that PsA can be as severe as RA (26). In particular, Sokoll *et al.* demonstrated that although joint damage is significantly greater in RA than PsA, disability and quality of life scores are similar in both disorders (27). There is no data on the economic impact of PsA in Italy, but an US study estimated the direct costs of psoriasis and PsA to average $650 million in 1997 (28). 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 Centers estimated that direct and indirect costs related to PsA average 2,264 and 4,599 per patient/year, respectively (29).

Anti-TNF-α therapy in psoriatic arthritis

Three anti-TNF-α compounds are licensed for use in rheumatic inflammatory conditions in Italy. 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-α receptor linked to the Fc portion of a human IgG1, is administered subcutaneously at a dose of 25 mg twice weekly. Infliximab (Remicade®, Centocor, Malvern, PA, US), a chimeric human-murine monoclonal anti-TNF-α IgG1 antibody, is administered intravenously at a dose of 3-5 mg/kg, and is always used in combination with methotrexate. Adalimumab (Humira®, Abbott Laboratories, Abbott Park, IL, US) is a novel fully humanized monoclonal anti-TNF-α antibody, which is usually administered subcutaneously at a dose of 40 mg every other week. All these agents can exert powerful anti-inflammatory effects by binding and inactivating soluble and cell-bound TNF-α. At the present, only one TNF-α blocking agent, etanercept, is licensed for use of active, recalcitrant PsA in Italy (level of evidence A), but there is mounting evidence supporting the efficacy of infliximab (level of evidence A) and adalimumab (level of evidence A) as well.

Etanercept

Etanercept (25 mg etanercept subcutaneously twice weekly) has recently been evaluated in a 12-week RCT versus placebo in 60 patients with PsA and psoriasis (20). All patients had active PsA (defined as 3 swollen joints and 3 tender or painful joints) at the time of study enrollment. 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 (30). 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 annualized 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. 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 (31-34).

Etanercept has officially been approved for use in active recalcitrant PsA by the European Agency for the Evaluation of Medicinal Products (EMEA) in December 2002 and by the Federal and Drug Administration (FDA) in August 2003.

Infliximab

There have been numerous reports and open studies evaluating infliximab in active PsA, but only two RCT (IMPACT (Infliximab Multinational Psoriatic Arthritis Controlled Trial) and IMPACT2). The first RCT, IMPACT involved 101 patients with active PsA (defined as affecting at least 5 active joints) (35). Patients were randomized to receive infliximab at a dose of 5 mg/kg or placebo. 69% patients in the infliximab group met the ACR20 response criteria, compared to only 8% in the placebo group. Similarly, among those treated with infliximab, 25 patients (49%) achieved ACR50 and 15 patients (29%) achieved ACR70. The average reduction of the PASI was 81% in the infliximab group compared to an average increase of 36% in the placebo group.

So far, data on radiographic progression measured by modified van der Hejde Sharp score has only been reported in abstract form (36). The annual x-ray progression rate was reduced by infliximab from a predicted rate of 5.8 points per year to 0.05 in the placebo/infliximab group and -1.52 in the active treatment group (36).

In the IMPACT2 trial, 200 PsA patients with active PsA and at least one plaque of psoriasis were randomized to receive infliximab 5 mg/kg or placebo (37). 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 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 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 those of numerous reports and open trials published so far.

Van den Bosch *et al*. evaluated in a 3-month open study the efficacy and safety of infliximab (5 mg/kg) versus placebo in 40 patients with active SpA, 13 of whom had PsA (38). The primary end points were the improvements in patient and physician global assess-

ments of disease activity on a 100-mm visual analog scale. Both primary end points improved significantly in the infliximab group compared with the baseline value, with no improvement in the placebo group. There was one drug-related case of disseminated tuberculosis.

In 54-week, open-label study, 10 patients treated with infliximab (5 mg/kg at weeks 0, 2, 6 and at individualized doses after week 10) achieved all a ACR20 response by week 2, while 8 patients achieved a ACR70 response at week 10 (21). In addition, PASI was also reduced by 71.3%. There were no significant adverse events such as severe infections or infusion reactions.

An Italian study of 30 weeks' duration confirmed that infliximab at 3 mg/kg was effective and well tolerated in 16 patients with peripheral active PsA with at least 6 months of previous methotrexate therapy (22). In particular, at week 30, the percentages of patients achieving the ACR20, 50 and 70 response rates were 64%, 57%, and 57%, respectively. In the 3 patients with active axial disease, spinal stiffness and pain resolved almost completely at week 2. PASI improvement was 86% at the end of the study. Two patients discontinued the therapy due to allergic reactions.

On the same line, an open-label, 6-month study of 12 patients with active PsA (11 with predominant peripheral arthritis) resistant to conventional DMARD treatment showed that infliximab (5 mg/kg) combined with methotrexate was effective in controlling disease activity. At week 26, 10 patients met the ACR20 criteria; 6 of them also met the ACR50, and 4 the ACR70. Infliximab was well tolerated in all patients and no infusion reactions were observed (39).

A 22-weeks open study assessed the response of 9 patients with both active psoriasis and PsA to 5 infusions of 3 mg/kg infliximab (40). This study demonstrated that ACR 20/50/70 response was achieved in 89%/56%/22% of cases, respectively, while the mean PASI score significantly improved from 19 to 4.

Finally, in an observational study on 16 patients with DMARD-resistant, active PsA treated with infliximab (5 mg/kg) the swollen joint count improved significantly at week 54 while PASI improved significantly at week 14 (41).

Adalimumab

A 24-week, placebo-controlled, double-blind, phase III study evaluated the therapeutic effects of adalimumab (40 mg subcutaneously every other week) in 315 patients with active, NSAID-resistant PsA (42). Active disease was defined by the presence of at least 3 tender and swollen joints. At 24 weeks, 57% of the study completers treated with adalimumab reached an ACR20, 39% reached an ACR50, and 23% achieved an ACR70 response. By contrast, of the study completers treated with placebo, 15% reached an ACR20, 6% reached an ACR50, and 1% achieved an ACR70 response. Among the 69 adalimumab-treated patients evaluated with the Psoriasis Area and Severity Index (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. Adalimumab was generally safe and well-tolerated, with a similar incidence of adverse reactions compared with that in the placebo group.

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 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. Anti-TNF-α agents have proved effective in AS, a condition belonging to the SpA like PsA and similar to psoriatic spondylitis. 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. Finally, the potential long-term effects of TNF-α blockers are still unknown.

The objective of these guidelines is to provide the evidence for the optimal use of anti-TNF-α therapy in patients with PsA in Italy. 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 who have the most to gain from anti-TNF-α therapy receive this treatment; to guarantee that use of anti-TNF-α agents be undertaken only by experienced rheumatologists in specialized centers; to avoid improper use of these agents that could lead to patients' harm and economic burden on the society; and to monitor both clinical response and adverse events by common parameters across different centers.

Another goal is 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; and preservation and improvement of quality of life and of life expectancy.

At the present, there are no health economic studies addressing the role of anti-TNF-α therapy in PsA. Until such data becomes available, the benefit conferred by anti-TNF-α treatment has to be weighted against the elevate costs of TNF-α blockade. These guidelines are based on the principle "to maximize the health gain (...) within the constraints of available resources and equity concerns" (43).

Therapeutic schedules

It has been proposed (44, 45) 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 (46)). However, the initial evidence accrued so far in the treatment of the spondyloarthropathies does not appear to support this contention (47, 48). We thus feel that, in the absence of definite evidence, suggestions to use therapeutic regimes different from those that are recommended cannot be endorsed.

Inclusion criteria

To be eligible for treatment with anti-TNF-α agents, patients should have active PsA. There are no validated, widely accepted classification criteria for PsA (49), but a diagnosis can usually be made either when patients have arthritis and psoriasis or, in the absence of psoriasis, if at least a first-degree relative is affected by psoriasis.

Traditionally, PsA is stratified in 5 clinical subgroups according to the Moll and Wright criteria (50). However, this classification does not include subsets of PsA that are now well recognized, such as psoriatic enthesitis and/or dactylitis (51). 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 (52). According to a recent re-evaluation, only two of the subgroups identified by Moll and Wright appear to be really distinct, psoriatic spondylitis (with or without peripheral arthritis) and peripheral arthritis in the absence of axial disease (53). These two subgroups are characterized by different response to therapy, because psoriatic spondylitis is typically unresponsive to treatment with DMARDs such as sulfasalazine and methotrexate. Therefore, for therapeutic purposes, we elected to stratisfy PsA according to the following three subsets depending on the predominant involvement: a) PsA with peripheral arthritis, b) PsA characterized by enthesitis and c) psoriatic spondylitis.

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

They have not responded to full therapeutic or tolerated doses (unless contraindicated) of at least 2 NSAIDs over 3 months, to at least two steroid injections (in cases of mono- or oligoarthritis) as well as to at least two of the DMARDs most commonly used in PsA (methotrexate, ciclosporin, sulfasalazine, leflunomide), administered alone or in combination for at least three months (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 ciclosporin, and 20 mg per day for leflunomide)

plus

They have at least one swollen joint; there is a favorable expert opinion (as defined in "Assessment of response to, and criteria for withdrawal of anti-TNF-α therapy" below); and they fulfill at least 1 of the following 2 criteria: BASDAI 40 mm (VAS 0-100 mm) and/or at least 3 tender joints.

PsA characterized by enthesitis. Anti-TNF-α therapy should be considered in patients with PsA characterized predominantly by peripheral enthesitis if:

They have not responded over a 3-month period to maximal doses of at least 2 NSAIDs and at least 2 DMARDs as well as to local steroid therapy (at least 2 steroid injections); there is a favorable expert opinion

plus

They fulfill both of the following criteria: Tenderness over inflamed entheses 2 on a 0-4 Likert scale and BASDAI 40 mm (VAS 0-100 mm).

Psoriatic spondylitis. Anti-TNF-α therapy should be considered in patients with PsA characterized predominantly by axial involvement (sacro-iliitis and/or spondylitis) in agreement with the recommendations recently proposed by the International ASAS (Assessment in Ankylosing Spondylitis) working group (54) if:

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

plus

They fulfill both of the following 2 criteria: Favorable Expert Opinion and BASDAI 40 mm (VAS 0-100 mm).

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, these agents should not be administered during pregnancy and lactation. Patients who become pregnant during treatment should discontinue anti-TNF-α agents as a matter of precaution. In addition, anti-TNF-α agents are controindicated in any of the following conditions:

- known hypersensitivity to a specific anti-TNF-α agent;
- sepsis or high risk of developing sepsis;
- active infections including HIV and AIDS;
- previous TB not adequately treated;
- neoplasms over the last 10 years (except for basal cell carcinoma);
- heart failure class III or IV according to the 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 (55-57).

Monitoring of disease activity

It has previously been demonstrated that active joint count can reliably assess disease activity in PsA characterized by predominant peripheral joint involvement (58). The most widely used measure of drug efficacy in clinical trials are the ACR response criteria which have been validated for use in PsA increasing the total number of joints counted to 78 for tenderness and 76 for swelling (59). Thus, we elected to use the ACR response criteria for evaluation of peripheral arthritis in

PsA. There is no validated measure to clinically assess dactylitis, but since dactylitis is due to tenosynovitis sometimes associated with joint synovitis (60), we propose that the joints of a digit with acute dactylitis be counted as active joints. With regard to enthesitis, we elected to use for the purpose of clinical assessment the Maastricht ankylosing spondylitis enthesis score (MASES), a validated index which includes thirteen common sites of entheseal involvement (61). Finally, we propose to assess psoriatic spondylitis using the outcome variables outlined in the International ASAS consensus statement for the use of anti-TNF-α agents in AS (54). We recognize that psoriatic spondylitis is usually less severe than that of AS. Therefore, it is possible that measures of axial disease originally developed for AS may not be sufficiently sensitive to change or accurate for use in PsA with axial involvement. However, unless or until more specific measures for assessment of psoriatic spondylitis are developed, we recommend that the ASAS guidelines be followed, in agreement with the British Society for Rheumatology (BSR) guidelines for anti-TNF-α therapy in PsA (62).

Since the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), a composite measure that can theoretically capture overall disease activity, has been shown to highly correlate with patient perception of disease activity and to perform similarly for axial and peripheral PsA, we also propose to use this index in the assessment of patients of PsA (63). On a note of caution, given the rather poor correlation between the BASDAI and external indicators of disease activity, such as treatment decisions, we think that the BASDAI should always be used in conjunction with other indices as already recommended by other authors (63). Finally, we believe that until more specific, validated tools for monitoring disease activity in PsA become available, a full clinical assessment of peripheral joints using the 78-tender and the 76-swollen joint count as described elsewhere (59), of the entheses, and of spinal disease should be performed. In particular, in order to assess the response to anti-TNF-α therapy, we recommend that disease activity be monitored using the following parameters whenever appropriate:

- Tender joint count;
- Swollen joint count;
- Pain on VAS scale;
- Patient's global assessment of disease activity;
- Physical function (Health Assessment Questionnaire);
- MASES (Maastricht Ankylosing Spondylitis Enthesis Score) (for patients with enthesitis);
- 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 (64).

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 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.

In PsA with peripheral arthritis: 20% reduction in the number of tender and swollen joints and 20% improvement of at least 3 of the remaining ACR20 criteria in patients with psoriatic polyarthritis (5 affected joints); the response of patients with DMARD-resistant mono- or oligoarthritis at baseline should be assessed on an individual basis; and expert opinion that anti-TNF-α therapy should be continued

In PsA characterized by enthesitis: 20% reduction in the MASES in patients with at least 3 clinically inflamed entheses at baseline; 50% relative or two-point absolute improvement in the BASDAI score assessed on an numerical rating scale (equivalent to 20 mm on a 100-mm VAS); and expert opinion that anti-TNF-α therapy should be continued

In psoriatic spondylitis: 50% relative or two-point absolute improvement in the BASDAI score assessed on an numerical rating scale (equivalent to 20 mm on a 100-mm VAS); and expert opinion that anti-TNF-α therapy should be continued.

Withdrawal of treatment

We recommend that assessment of response, and consideration whether anti-TNF-α therapy should be discontinued, be undertaken after three months after therapy onset. Anti-TNF-α therapy should be discontinued in the following instances.

PsA with peripheral arthritis: If in the opinion of the expert no clinically significant improvement has occurred, and if the ACR20 response has not been achieved in patients with psoriatic polyarthritis (5 affected joints) at baseline.

PsA characterized by enthesitis: If in the opinion of the expert no clinically significant improvement has occurred; in the absence of ≥ 50% relative or two-point absolute improvement in the BASDAI score assessed on an numerical rating scale (equivalent to 20 mm on a 100-mm VAS); and in the absence of ≥ 20% reduction in the MASES in patients with at least 3 clinically inflamed entheses at baseline.

Psoriatic spondylitis: If in the opinion of the expert no clinically significant improvement has occurred, and in the absence of ≥ 50% relative or two-point absolute improvement in the BASDAI score assessed on an numerical rating scale (equivalent to 20 mm on a 100-mm VAS).

Withdrawal 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 or demyelinating disease;
- development of neoplasm;
- development of serious intercurrent infection (withdrawal may be temporary);
- pregnancy (withdrawal may be temporary);
- surgical procedures (temporary withdrawal).

Treatment centers 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 specialized centers, namely university clinics and rheumatology units in hospitals.

The Italian Society of Rheumatology is committed to organize *ad hoc* training courses for Rheumatologists, to create a national register of treated patients, and to appoint qualified experts to audit the prescribing and monitoring practices.

Updates of the recommendations

The Italian Society for Rheumatology will implement regular updates of these recommendations on the basis of the results of new clinical studies and of data from post-marketing surveillance. Any of the statements made herein may be modified on the basis of new clinical and pharmacoeconomic data and long-term safety considerations. These recommendations have been slightly modified from those produced earlier (65) to incorporate the emerging evidence in this rapidly expanding field as well as the feedback provided by rheumatologists with a special interest in PsA. However, they are broadly consistent with the previous version published in Italian (65).

Methods

We searched the Medline for published studies using the key words "psoriatic arthritis", "infliximab", "etanercept", "adalimumab", and "tumor necrosis factor (subheading: antagonists and inhibitors)". We also reviewed relevant abstracts of the annual meetings of the American College of Rheumatology (ACR) as well as abstracts of the European League against Rheumatism (EULAR) from 2002 to 2004.

We used the following levels of evidence, which have been developed by the US Agency for Health Care Policy and Research (AHCPR, now the US Agency for Health Research and Quality, AHRQ) (66):

Ia Evidence obtained from meta-analysis of randomized controlled trials.

Ib Evidence obtained from at least one randomized controlled trial.

IIa Evidence obtained from at least one well-designed controlled study without randomization.

IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.

III Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlational studies, and case studies.

IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendations

A. Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (evidence levels Ia, Ib)

B. Requires the availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation. (evidence levels IIa, IIb, III)

C. Requires evidence obtained from expert committee reports or opinions and⁄or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (evidence level IV).

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