Psoriasis and psoriatic arthritis: Immunological aspects and therapeutic guidelines

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ABSTRACT

Psoriasis is an inflammatory skin disease that affects 1-3% of the European population. Chronic plaque psoriasis, the commonest form of the condition - affecting the majority of patients - usually manifests as red, heavily scaled plaques on elbows, knees, scalp and lower back, but any skin surface may be affected. Psoriasis is associated with an inflammatory sero-negative arthritis, namely "psoriatic arthritis", in approximately 15% of patients with psoriasis and occurs more commonly in people with inflammatory bowel disease such as patients with Crohn's disease.

Several studies have demonstrated the role of genetic predisposition, innate and adaptive immunity in the pathogenesis of psoriasis. There is considerable evidence that innate immunity and specifically a dysregulation of the innate immune response is central to the development of psoriasis. The role of TNF-α is particularly intriguing. The evidence includes further observations that a variety of anti-TNF approaches such as monoclonal antibodies and fusion proteins of soluble TNF receptors are effective therapies both in psoriasis and psoriatic arthritis. In this review, in addition to pathogenetic aspects, some preliminary guidelines for the use of anti-TNFα therapy in patients with psoriasis and psoriatic arthritis will be discussed.

Introduction

Psoriasis is a chronic recurrent disease of variable severity that affects between 1% and 3% of the population, is associated with an inflammatory sero-negative arthritis - "psoriatic arthritis", - in approximately 15% of patients. The key histological features of psoriasis have been appreciated for at least one hundred years: these are epidermal keratinocyte hypoproliferation; dermal vascularity; and an inflammatory infiltrate.

Over the last few years the role of some genes, for example HLA-Cw6, as well as the role of the immune system in the development of psoriasis, have become more defined.

It has been demonstrated that innate immunity plays a key role in the development of psoriasis, particularly through the production of some cytokines, among which TNFα is one of the most important. This molecule has become the target of new therapeutic approaches which are effective in controlling psoriasis and psoriatic arthirits.

This review is focused on the contribution of some genes, HLA and non HLA linked, and others immunological mechanism in the pathogenesis of the disease. Moreover, the clinical manifestations and the guidelines for the treatment of psoriasis and psoriatic arthritis, including new "biological" agents, are discussed.

Genetic aspects of psoriasis

Psoriasis is a common inflammatory skin disease that affects approximately 2% of the European population (1). Chronic plaque psoriasis, the commonest form of the condition - affecting 80% of patients - manifests usually as red, heavily scaled plaques on elbows, knees, scalp and lower back, but any skin surface may be affected. Although rarely life-threatening psoriasis causes considerable psychosocial disability and impairment of quality of life for those it afflicts. Most cases (75%) present before the age of 40 (type I psoriasis) with a second peak of onset between the ages of 55 and 60 years - type II psoriasis. Clinically there is little to distinguish type I from type II disease. As a general observation type I psoriasis is familial, severe and has a strong association with HLA-Cw6. Type II

psoriasis is neither familial nor associated with HLA-Cw6 (1). Considerable research interest is invested in understanding the immunogenetics of psoriasis; to date at least 8 psoriasis susceptibility (PSORS) loci have been identified but no gene or gene product (2). Researchers are however in agreement that in caucasian populations PSORS 1, located at chromosome 6p21.3 (3), which may or may not be HLA-Cw6, is a key determinant of disease expression. Proteins identified within the PSORS 1 region and which may have relevance to expression of disease are corneodesmosin and helical coiled rod (HCR). PSORS 4 located on chromosome 1q21, is a region encoding for genes important in epidermal differentiation. This is an important observation for a disease in which keratinocyte hypoproliferation and loss of differentiation are key characteristics (3). It is probable that investigations will reveal that what is currently labelled clinically as chronic plaque psoriasis vulgaris will turn out to be several genotypically distinct but phenotypically similar dermatoses. Studies of monozygotic twins reveal a concordance of 72% for psoriasis thereby implying a necessity for an environmental factor to trigger development of skin lesions in genetically predisposed individuals. Environmental triggers known to induce psoriasis in this way include β-haemolytic streptococcal infection, HIV, drugs such as β blockers and stress (1).

Innate and adaptive immunity in psoriasis

Until the early 1980s prevailing dogma as to psoriasis pathogenesis suggested that the disease was primarily one of epidermal keratinocytes and that the aforementioned histological features, such as inflammation, were secondary. At that time evidence began to emerge that psoriasis was initiated and probably maintained by activated (HLA-DR +) T cells - with predominance of $CD4^+$ T cells in the dermis and $CD8^+$ T cells in the epidermis. Other lines of evidence that psoriasis was cell-mediated came from observations that the disease could be "transmitted" or "cured" by bone marrow transplant and that therapies targeted at T cells specifically such as cyclosporin and an interleukin - 2 diphtheria fusion toxin, which is cytotoxic for lymphocytes and not keratinocytes, are effective treatments for the disease. T cells within a plaque of psoriasis are predominantly of the memory - effector $CD45RO^+$ subset and are cutaneous lymphocyte associated antigen positive. Linked to the T cell hypothesis was the finding that cytokines contributing to the pathogenesis of the disease are mainly of the TH1 subtype with a predominance of interleukin 2 and interferon -γ. Based on the T cell hypothesis of psoriasis, biological therapies targeting T cells specifically efalizumab (anti-CD11a) and alefacept (an LFA3 fusion protein targeting CD2) have been developed and licensed for the treatment of psoriasis (4).

In the late 1990s and to the present day a shift in our understanding of the immune mechanisms in psoriasis underwent a step change in a serendipitous fashion. This came in the form of the observation that a patient who had fistulating Crohn's disease and concomitant psoriasis received infliximab (a chimeric monoclonal antibody to TNF-α) for her Crohn's disease and she experienced a complete and rapid improvement of the co-existing psoriasis (5). This observation brought the role of TNF-α into focus as a key pro-inflammatory cytokine in psoriasis. There is considerable evidence that innate immunity and specifically a dysregulation of the innate immune response is central to the development of psoriasis (6). Evidence includes further observations that a variety of anti-TNF approaches such as monoclonal antibodies and fusion proteins of soluble TNF receptors are effective therapies (7). Cellular and humoral components of innate immunity are upregulated and/or activated in chronic plaque psoriasis. For example, plaques comprise proliferation of the epidermal barrier – a prime innate immune response, increased numbers of neutrophils, phagocytes and dendritic cells (both myeloid and plasmacytoid) and natural killer T cells. Humoral components of the innate immune response probably involved in psoriasis pathogenesis are increased i.e. endogenous antimicrobial peptides such as β defensin and cathelicidins, activation of the complement cascade; elevation of pro-inflammatory cytokines including TNFα and interleukin-1β and chemokines including interleukin-8 and RANTES. There is no good animal model for psoriasis but a recently developed mouse model includes transplantation of uninvolved psoriasis skin onto the flanks of AGR 129 mice (8). These mice are deficient in T and B cells as well as natural killer cells. The transplanted uninvolved skin develops into psoriasis with histological features of acanthosis and T cell proliferation. Interestingly and key to the innate immune hypothesis, is the observation that blockade of TNF-α activity in this model inhibits the clinical, histological and Tcell proliferative changes.

Autoantibodies in psoriasis

There is to my knowledge no good evidence that an antigen or autoantigen has been reliably identified in psoriasis although a number of candidates including superantigen, HPV, hidden stratum corneum autoantigen and keratin 17 have not been shown to be viable. Neither has corneodesmosin. This observation supported by the recent demonstration that a single nucleotide mutation in the PTPN22 gene, which is important in autoimmunity and associated with diseases such as diabetes mellitus type I and rheumatoid arthritis, is not associated with chronic plaque psoriasis (9). Thus, it is likely that inflammation of psoriasis is a balance between the adaptive i.e. T-cell mediated immune response and the innate immune response. This was perhaps a survival mechanism in the pre-antibiotic era which allowed patients to survive streptococcal or other infections but with the downside of developing psoriasis. The only reliable way to take this observation forward is to move from the old reductionist cascade view of biological systems to the integration of quantitative chemistry to systems biology.

Psoriasis and the joints

Psoriasis is associated with an inflammatory sero-negative arthritis, namely

psoriatic arthritis (PsA) in approximately 15% of patients and occurs more commonly in people with inflammatory bowel disease in that approximately 10% of patients with Crohn's disease also suffer from psoriasis.

PsA is classified among the spondyloarthritides. The spondyloarthritis (SpA) complex also includes ankylosing spondylitis (AS), reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD) and forms that fail to meet established criteria for definite categories, which are designated as undifferentiated SpA (uSpA). With regards to PsA, it is well recognized that there are different subtypes some of which are not part of the SpA complex. Five clinical subtypes of psoriatic arthritis are recognized: 1. Predominant involvement of the distal interphalangeal joints. As an isolate finding, arthritis of the interphalangeal joints occur in 8-10% of cases. 2. Arthritis mutilans. It is fortunately rare. There is a marked osteolysis of the phalanges, metacarpals or metatarsals. 3. Symmetric polyarthritis similar to rheumatoid arthritis. Compared with rheumatoid arthritis, there is a tendency to bone ankylosis of the distal and proximal interphalangeal joints. 4. Oligoarticular arthritis. There is an asymmetric involvement of scattered small and large joints. "Sausage-like" digit or dactylitis is due to flexor tenosynovitis. Joint involvement is possible but is not an indispensable condition for the "sausage-shaped" feature. 5. Axial involvement similar to primary AS.

Several methodological difficulties have impeded epidemiological studies on PsA. First of all, there is a lack of internationally accepted criteria for the diagnosis of PsA that are able to define the large spectrum of the disease. The CASPAR (ClASification Criteria for Psoriatic ARthritis) group have compared existing classification criteria for PsA in a large international cohort including 589 consecutive attendees with PsA and 535 control patients (next clinic attendee with inflammatory arthritis) from 29 rheumatology clinic in 12 contries (10). The diagnosis was based upon the physician's opinion and verified by an examination of randomly select case-record forms by the data quality committee. Subjects were classified by each of the 7 existing criteria (Moll & Wright, Bennett, Vasey & Espinoza, ESSG, Gladman, McGonagle, Fornie). The criteria-set of Vasey and Espinoza appeared to be the most accurate. The authors suggested that it could be improved by incorporating other features with high diagnostic odds ratios. The CASPAR group also aimed to see whether more accurate criteria could be derived from examination of the observed patient data. The group have proposed its own criteria, i.e. the CASPAR criteria. These are more specific (98.7%) than Vasey and Espinoza criteria but less sensitive (91.4%). The new criteria should be adopted for future clinical and epidemiological studies of PsA.

Little information is available about racial or ethnic differences in the occurrence of PsA. Ethnicity affected the development and expression of PsA in a series of patients from Singapore (11). Indians having psoriasis had double the risk of developing PsA compared to Chinese suffering from the same disease. Furthermore, lumbar spondylitis when present in Chinese subjects was asymptomatic in 45%, being detectable only by radiological examination.

Two recent population-based studies have evaluated the incidence and prevalence of PsA. The average age and sex adjusted incidence rate per 100,000 people in Olmsted County, Minnesota, USA was 6.59, while the prevalence for January 1, 1992, was about 1 per 1000 (12). The annual incidence in a Finnish population was estimated to be 6.1 per 100,000 adults (13). The peak incidence occurred in the 45-54 year age range. In both studies the male to female ratio was around 1:1.

The majority of PsA studies have been performed in order to evaluate the frequency of arthritis in psoriatic patients. The data are discordant, with the frequency of PsA varying from 7% to 42% (14-17). Some studies, reporting a high frequency of PsA comprised patients with psoriasis who were hospitalized and are therefore biased in selection of patients. Differing methods of patient identification is another factor that can explain these discordances.

An Italian study evaluated the frequency of PsA in a series of unselected patients with psoriasis (17). Twenty-six percent of the patients were considered to have PsA. Oligoarthritis, present in 59% of the PsA patients, was the most common pattern of arthritis. Thirteen per cent had inflammatory spinal pain and 8% had radiological evidence of sacroiliitis (bilateral grade 2-4 or unilateral grade 3-4). In Korean patients with psoriasis the prevalence of PsA was 9% (18). Spondylitis was the most common pattern (50%). In a multicentric American study, including a large series of patients with PsA, the prevalence of radiological evidence of sacroiliitis (grade 2 or higher) was 78% (19). In an outpatient clinic in Toronto, Ontario, Canada, Wong *et al*. studied the mortality risk of their patients with PsA (20). These authors found the standardized mortality ratios to be 1.59 for women and 1.65 for men, indicating 59% and 65% increases in the death rates compared to the general population of Ontario. Deaths caused by respiratory disease were particularly higher in these patients. Evidence of previously active and severe disease, as manifested by the prior use of medications and by radiological changes as well as an elevated ESR at presentation, were prognostic indicators for death (21). This study is probably limited by a selection bias of patients having a more severe disease, which led to an overestimate of the mortality risk for PsA. In contrast the Mayo Clinic population-based study did not observe any difference in survival between the inceptional cohort of PsA patients and the general population (12).

The synovitis, acne, pustolosis, hyperostosis, and osteomyelitis (SAPHO) syndrome shares manifestations and clinical association with the SpA complex. The name was proposed in 1987 by Chamot and co-workers who were impressed by the association of hyperostosis (frequently involving the anterior chest wall) with various skin lesions. Psoriasis has been suggested to be the missing link between SAPHO syndrome and SpA (22). There are no data on the prevalence and incidence of this syndrome.

Guidelines in the treatment of cutaneous psoriatic manifestations

In recent years, clinical practice guidelines have been advocated as a means to reduce variability with care and to improve clinical performance (23). Guidelines should be developed by multidisciplinary, nationally representative groups. A systematic review should be undertaken to identify and critically appraise the literature. Recommendations should be explicitly linked to the supporting evidence. To be effective instruments for change, clinical guidelines must be coupled with active implementations strategies that promote provider acceptance. In spite of the use of the term "guidelines" for several documents concerning the treatment of psoriasis, only a few ones may represent true "guidelines" according to the principles mentioned above. The purpose of this paragraph is to review the evidence for treatment options available for psoriasis and to underline problems for their application in clinical practice (24).

Psoriasis is a chronic, recurrent disease of variable severity that affects between 1% and 3% of the population. The severity of psoriasis traditionally has been evaluated by objective measurement of the extent of the body surface affected and consideration of the subtype of psoriasis, degree of disability, and feasibility of topical therapy. Clinical measures of severity do not necessarily reflect the potentially serious impacts of psoriasis on patients' quality of life (25, 26).

Although topical preparations may be sufficient to control psoriasis symptoms in patients with relatively mild disease, patients with moderate to severe disease usually require phototherapy or systemic agents to achieve good clearance. Potentially serious toxicities can limit their long-term use and may necessitate rotation of therapies and/or treatment regimens.

Traditional therapies currently approved in various countries across Europe for the treatment of moderate to severe psoriasis include narrowband ultraviolet B radiation (NBUVB), photochemotherapy (oral psoralen plus ultraviolet A radiation – PUVA), cyclosporin, methotrexate, and oral retinoid therapy (27, 28). Other systemic therapies, such as hydroxyurea or fumaric acid esters, are approved in a very small number of European countries or may be used off-label for the treatment of psoriasis. Treatment of moderate to severe psoriasis is often initiated with narrowband and/or broadband ultraviolet B (UVB) followed by PUVA. Combination and rotation of several treatments (topical, phototherapy and systemic) is common, although empirical (29, 30). In some countries (Austria, Denmark, Netherlands, Portugal), methotrexate is often prescribed only as a last resort; however, in other countries (Belgium, Luxembourg, France, UK), methotrexate is used as a first-line systemic treatment for severe psoriasis. In Germany, Italy, France and many other countries, methotrexate is used if concomitant acute psoriatic arthritis is observed. In Italy, where cyclosporin is the most commonly used systemic therapy for psoriasis, methotrexate is usually reserved for treatment of patients resistant to classical therapies. Physicians in some countries (France, UK) combine cyclosporin with methotrexate. Retinoids seem to be the last choice in several European countries and are usually used in combination, since monotherapy appears to have suboptimal efficacy for chronic plaque psoriasis. Accurate comparison of the efficacy of therapies for moderate to severe psoriasis is limited by the scarcity of comparative clinical trials. A European survey of psoriasis clinical trials published between 1977 and 2000 found that only 6 of 75 randomized trials of systemic therapy (8.0%) were comparative studies of treatments from different therapeutic classes, and only 2 trials compared 2 or more systemic therapies (cyclosporin versus etretinate in both trials) (24).

Recently, a number of new agents have been added to the above referenced options. These have been collectively termed as "biologicals" and include two main groups, i.e., T-cell targeting agents (alefacept and efalizumab) and TNFα antagonists (etanercept, and infliximab). To date, only placebo-controlled randomized controlled trials (RCTs) have been conducted (31, 32). Additional pieces of information are needed, including estimates of the rate of relapse on drug withdrawal, identification of predictive factors for treatment failure and more reliable and extensive data on drug safety with special emphasis on adverse events with an incidence lower than 1% (which implies collecting data on drug exposure from more than 10,000 people). Comparative effectiveness is also of concern. In consideration of the limited data available, these new drugs should be better introduced in the market conditional to systematic collection of post-marketing data on effectiveness and safety. Examples of such surveillance programmes are the BAD Biological Therapy Register in the United Kingdom and the project Psocare in Italy (33).

Guidelines in the treatment of psoriatic arthritis

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 (34, 35) In addition, in approximately 20-40% of patients, PsA can also affect the axial skeleton (so-called "psoriatic spondylitis") (36), leading to functional limitation and deformity akin to, although usually less severe than that observed in AS (37).

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 antirheumatic 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 cyclosporin (level of evidence B), but their efficacy in inhibiting articular erosions has not been assessed in proper controlled studies (reviewed in 38–41). 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. In addition, none of these agents has proved effective in ameliorating the symptoms of psoriatic spondylitis, including pain and early morning stiffness. 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) (42), 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-TNFα agents) has been shown to inhibit joint erosions in RA. Anti-TNFα 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 and able to inhibit joint damage in PsA (43-47).

Preliminary guidelines for clinical use of anti-TNFα therapy

The Italian Society of Rheumatology has proposed some preliminary guidelines for the clinical use (48, 49) of anti-TNFα agents. To be eligible for treatment with anti-TNFα agents, patients should have active PsA. There are no validated, widely accepted classification criteria for PsA, 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.

For therapeutic purposes PsA is stratified 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. Therapeutic guidelines are summarized in Table I.

It is recommended 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-TNFα 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-TNFα agents as a matter of precaution. In addition, anti-TNFα 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 and demyelinating disorders.

Table I. Guidelines for the use of anti-TNFα agents in psoriatic arthritis.

	Response to DMARDs	Clinical parameters
PsA with peripheral arthritis	No response 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)*	- Have at least one swollen joint -Favorable Expert Opinion (as defined in "Assessment of response to, and criteria for withdrawal of anti-TNF-α therapy" , see Table II) plus - BASDAI ≥ 40 mm (VAS 0-100 mm) or - Have at least 3 tender joints
PsA characterized by enthesitis	- No response 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)	- Favorable Expert Opinion plus -Tenderness over inflamed entheses ≥ 2 on a 0-4 Likert scale or - BASDAI ≥ 40 mm (VAS 0-100 mm)
Psoriatic spondylitis	In agreement with the recommendations recently proposed by the International ASAS (Assessment in Ankylosing Spondylitis) working group if: - No response over a 3-month period to maximal doses of at least 2 NSAIDs	- Favorable Expert Opinion Plus - BASDAI ≥ 40 mm (VAS 0-100 mm)

* 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 cyclosporin, and 20 mg per day for leflunomide).

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.

Preliminary guidelines for assessment of response to anti-TNFα agents.

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 (50).

For anti-TNF-α therapy to be considered effective the criteria summarized in Table II should be satisfied.

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); and surgical procedures (temporary withdrawal).

Anti-TNF-α therapy is complex in that it requires a specific expertise in diagnosis, assessment of disease activity, drug administration (51), 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

Table II. Assessment to response to anti-TNFα therapy.

	Treatment should be continued	Treatment should be discontinued
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 - Expert opinion that anti-TNF-α therapy should be continued	- In the opinion of the Expert no clinically significant improvement has occurred, and - The ACR20 response has not been achieved in patients with psoriatic polyarthritis (≥ 5 affected joints) at baseline
PsA characterized by enthesitis	- ≥ 20% reduction in the MASES in patients with ≥ 3 clinically inflamed entheses at baseline and - ≥ 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) - Expert opinion that anti-TNF-α therapy should be continued	- 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) and - In the absence of ≥ 20% reduction in the MASES in patients with ≥ 3 clinically inflamed entheses at baseline
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) - Expert opinion that anti-TNF-α therapy should be continued	- 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)

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.

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