Infliximab in the treatment of plaque type psoriasis

Rosita Saraceno
Andrea Saggini
Lucia Pietroleonardo
Sergio Chimenti

Department of Dermatology, University of Rome Tor Vergata, Rome, Viale Oxford 81, Rome, Italy

Abstract: Psoriasis is a chronic and immunomediated skin disease characterized by erythematous scaly plaques. Psoriasis affects approximately 1% to 3% of the Caucasian population. Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine that plays a critical role in the pathogenesis of psoriasis. Infliximab is an anti-TNF-α drug widely used for the treatment of plaque type psoriasis and psoriatic arthritis. Controlled clinical trials demonstrated that infliximab is characterized by a high degree of clinical response in moderate to severe plaque psoriasis. Moreover infliximab showed rapid efficacy in nail psoriasis which represents a therapeutic challenge for dermatologists and a relevant source of distress for patients with plaque psoriasis. This anti-TNF-α has an encouraging safety profile, especially as long as physicians are watchful in prevention and early diagnosis of infections and infuse reactions. The efficacy, tolerability and safety profiles suggest infliximab as a suitable anti-psoriatic drug in the long-term treatment of a chronic disease such as plaque-type psoriasis.

Keywords: psoriasis, nail psoriasis, infliximab, long-term treatment

Introduction

Psoriasis is a chronic and immunomediated skin disease characterized by erythematous scaly plaques. Approximately 1% to 3% of the Caucasian population suffers from this disease.[1] Psoriasis entails a psychological morbidity comparable to other major chronic diseases such as heart disease, cancer and diabetes.[2] The most common clinical variant is plaque psoriasis, occurring in more than 80% of affected patients;[3] up to 40% of psoriatic patients develop an inflammatory deforming arthritis termed psoriatic arthritis (PsA).[4]

Traditional treatments for patients with moderate to severe plaque psoriasis include ciclosporin, methotrexate, acitretin, ultraviolet B (UVB), and ultraviolet A with psoralen (PUVA), both in monotherapy and combination. Ciclosporin is one of the most effective therapeutic options against psoriasis, even though long-term treatment is associated with hypertension and renal failure.[5] Similarly, methotrexate can lead to liver toxicity and pancytopenia.[6] Acitretin alone is only partially effective and rarely leads to a complete clearance of the skin lesions. Additionally, it produces substantial mucocutaneous toxic effects and, similarly to methotrexate, is teratogenic. UVB and PUVA both require an intensive treatment regimen (about 3 times per week prolonged for months), reducing patients' compliance. Additionally, PUVA has been associated with skin cancers.[7] The use of biological drugs can be seen as one of the greatest advances made in the treatment of psoriasis. These drugs have a selective action on receptors and mediators such as tumor necrosis factor alpha (TNF-α) which plays a key role in psoriasis.

Correspondence: Rosita Saraceno
Department of Dermatology, Policlinico Tor Vergata, Viale Oxford 81, 00133, Rome, Italy
Tel +39 06 26902743
Fax +39 06 20902742
Email rositasaraceno@yahoo.it

Pathogenesis and TNF-α

Both adaptive and innate immunity are involved in the pathogenesis of psoriasis. The disease is characterized by an abnormal skin proliferation due to complex interactions between immune cells and keratinocytes (KCs).[1] Psoriatic plaques are characterized by

an increased skin-homing activated T cells rate, expressing both lymphocyte function-associated antigen-1 (LFA-1) and cutaneous lymphocyte antigen (CLA);[8,9] CD4+ T helper-1 (Th1) cells, the newly described Th17 cells, and dermal CD11+ dendritic cells (DCs) down-regulate epidermal differentiation genes, leading to abnormal KC proliferation and parakeratosis.[10] The disease development depends on a mixed Th1/Th17 immune response inducing dermal DCs and macrophages to express mediators that favor inflammation and excessive KC proliferation, such as TNF-α and inducible nitric oxide synthase (iNOS).[10]

Several inflammatory mediators are overexpressed in psoriatic lesions, but only some of these have been shown to be of primary importance to the disease pathogenesis.[11] Among the cytokines whose levels are increased in psoriatic plaques, TNF-α seems to play a major role in this process; TNF-α, via activation of nuclear factor-κB (NF-κB), promotes the synthesis of numerous cytokines and chemokines such as IL-8 and IL-6.[12] In addition, TNF-α potentially contributes to the recruitment and accumulation of inflammatory cells, which are observed in both epidermis and dermis, by inducing the expression of intercellular adhesion molecule-1 (ICAM-1) on the surface of endothelial cells (ECs) and KCs. Of note, TNF-α upregulates ICAM-1 expression on the endothelial surface of microvessels, even though expression patterns differ between arterioles and venules. In venules, TNF-α leads to a further upregulation of ICAM-1 expression in the ECs already showing substantial ICAM-1 levels on their surface under normal conditions; by contrast, in arterioles the TNF-α-mediated endothelial upregulation of ICAM-1 correlates with a spatial variation of the ICAM-1 expression pattern among ECs. The TNF-α-dependent increase in the ICAM-1 endothelial expression produces quantitative and spatial variations in leukocyte-EC adhesion interactions in venules and leukocyte-EC rolling interactions in arterioles. These findings suggest that arterioles have an important role in the inflammatory cascade and that the spatial distribution as well as the expression levels of adhesion molecules in the microcirculation influence the timing and placement of leukocyte interactions and hence significantly affect the inflammatory response.[13]

Langerhans cells represent one of the main antigen presenting cells of the skin, inducing the activation of T cells. TNF-α is known to stimulate the migration of Langerhans cells to lymph nodes and to enhance the capability of presenting antigen to primed T cells.[14] TNF-α activity blockade results in a noticeable reduction in inflammation, keratinocyte proliferation and differentiation abnormalities in psoriasis. Effective treatment with TNF-blocking drugs rapidly down-modulates inflammatory dermal DC products TNF-α, iNOS, IL-20 and IL-23.[15]

Infliximab

Infliximab (Remicade®; Centocor, Inc.) is a recombinant immunoglobulin IgG1 chimeric antibody composed of human constant and murine variable regions that specifically binds to and blocks both trans-membrane and soluble TNF-α, but not lymphotoxin α (TNF-β). In vivo, infliximab quickly forms stable compounds with human TNF-α, a process that leads to the loss of the biological activity of TNF-α.[16] The binding between infliximab and TNF-α has a high affinity ($K = 4.5 \times 10^{-10}$M) leading to a temporary steric rearrangement of TNF-α when it is bound to infliximab, inhibiting the TNF-α from being recognized by its own receptor on the cell surface. Pharmacodynamic studies have shown the high affinity of infliximab that binds about 100% of TNF-α molecules after infusion.[16]

TNF-α is active as a homotrimer, but it is also found bound as a monomer, dimer or trimer to the surface of TNF-α-producing cells. Infliximab binds to all forms of soluble and membrane-bound TNF-α with high specificity. The concept that infliximab is also able to at least partially antagonize receptor-bound TNF-α is based on the high affinity of infliximab to TNF-α and on the documented high association-dissociation rate between TNF-α and TNF receptor.[16,17] Infliximab and TNF are multivalent proteins: in a situation of antigen excess, one of infliximab molecules can bind two different TNF trimers, whereas in case of antibody excess, three infliximab molecules can be bound to one TNF trimer. The high affinity, by means of the formation of large immune complexes, significantly reduces the chance of bioactive TNF dissociating from infliximab. The ability of infliximab to bind membrane-bound TNF-α in this fashion appears to be of central importance to explain the additional effects on TNF-α–producing cells (apoptosis, complement lysis, antibody-dependent cellular cytotoxicity), which have been described in vitro and in vivo and have been proposed to play a major role in enhancing the clinical efficacy of infliximab.[17,18] Infliximab might lead to the deletion of immune cells expressing TNF-α on their surface, such as macrophages/dermal DCs and T cells.[15]

Infliximab has been successfully used in psoriasis and in several off-label indications, such as hidradenitis suppurativa, pityriasis rubra pilaris and pyoderma gangrenosum among others.[19,20] This anti-TNF-α drug was developed for the treatment of various chronic inflammatory disorders mediated

by TNF-α and is approved for ulcerative colitis, adult and pediatric Crohn's disease, rheumatoid arthritis (RA), and ankylosing spondylitis.

Infliximab is administered as a short intravenous infusion over at least 2 hours at a total dose of 5 mg/kg body weight. According to the label for plaque psoriasis, infusions are given at weeks 0, 2, and 6 at the beginning (induction period) and then every 8 weeks for maintenance therapy. A single infusion of infliximab leads to a mean maximum serum concentration (C_{max}) of 118 μg/mL. The mean elimination half-life is approximately 8.5 to 9 days; however, depending on the dose and the duration of treatment, infliximab can be detected in the serum for up to 28 weeks.[21]

Clinical efficacy

Infliximab was tested in several clinical trials involving patients suffering from moderate-to-severe psoriasis, at variable doses of 3, 5 and 10 mg/kg of body weight;[22–24] in these studies infliximab treatment was shown to be generally well tolerated and resulted in a rapid and significant improvement in psoriatic signs and symptoms from baseline. Inclusion and exclusion criteria adopted in these phase II and III clinical trials were similar. Common inclusion criteria were: age ≥ 18 years, moderate-to-severe plaque-type psoriasis for at least 6 months, ineligibility or disease unresponsive to current conventional systemic treatments. Main exclusion criteria were: history of opportunistic or chronic/recurrent severe infections, internal malignancies or severe infectious diseases detected within 3 months prior to the start of infliximab treatment, drug-induced psoriasis, live vaccinations, clinically significant abnormal laboratory values, previous treatment with biological agents, systemic lupus erythematosus, demyelinating diseases, severe congestive heart failure, and non-cutaneous malignancies or lymphoproliferative diseases within the previous 5 years.

Patients had to be negative for latent tuberculosis, after specific screening including history, physical examination and purified protein derivative (PPD) skin testing; with the exception of non-medicated emollients and salicylic or tar shampoos, during the entire duration of the clinical trials patients were not allowed to apply any other treatment for psoriasis. Conventional systemic therapies were to be interrupted at least 4 weeks before the first infusion of infliximab, whereas topical treatments could be continued until 2 weeks before this time.

The overall efficacy of infliximab treatment was commonly assessed by the percentage of patients who achieved at least 50% and 75% improvement in Psoriasis Area and Severity Index (PASI) score (PASI 50 and PASI 75 respectively), the physician global assessment (PGA) and/or the body surface area score (BSA).

Phase II studies evaluated the safety and efficacy of infliximab in plaque psoriasis at different dosage regimens. In the phase II study,[22] 2 doses of infliximab (5 and 10 mg/kg), administered under a 3-dose induction regimen, were compared with placebo in 33 patients. Patients treated with infliximab showed a higher and more rapid degree of clinical improvement, as measured by PGA and PASI score, than patients receiving placebo; at week 10, PASI 75 was achieved by 82% and 73% of patients who received 5 and 10 mg/kg of infliximab, respectively, whereas such a result was observed in only 18% of patients treated with placebo (infliximab 5 mg/kg vs placebo $p = 0.0089$; infliximab 10 mg/kg vs placebo, $p = 0.03$). The end point of "excellent" or "clear" on PGA rating was achieved by 82% and 91% of patients in the infliximab 5 and 10 mg/kg groups, respectively, by contrast with 18% of patients in the placebo group (infliximab 5 mg/kg vs placebo, $p = 0.0089$; infliximab 10 mg/kg vs placebo 73%, $p = 0.0019$). Remarkably, patients receiving infliximab showed significantly higher mean percentage improvements in PASI score as early as week 2 ($p < 0.0003$), and their median time to response was 4 weeks. In relation to efficacy, there was no clinically significant difference between 5 and 10 mg/kg infliximab regimen, while according to the safety profile the 5 mg/kg regimen appeared to be preferable.

In the second phase II study,[23] the above-mentioned 3-dose induction regimen was further evaluated comparing 3 mg/kg with 5 mg/kg infliximab dose. This multicenter, double-blind, placebo-controlled trial was designed to assess the safety and efficacy of infliximab in 249 plaque psoriasis patients, presenting with BSA greater than 10%, in comparison with placebo; another aim of the trial was to test whether infliximab could safely be readministered to patients 20 weeks after completion of the induction regimen. Eighty percent of patients treated with infliximab, either 3 or 5 mg/kg, completed the 30-week study period, while this result was achieved by only 31% of the placebo-group patients. A rapid onset of response to the infliximab administration was observed in this trial, with a total of 34% of patients in the 3 mg/kg group and 40% of patients in the 5 mg/kg group achieving PASI 50 at week 2 versus only 4% of the placebo-treated patients ($p < 0.001$).

For both the infliximab groups, the maximum response was observed at week 10, when 72% and 88% of patients receiving 3 and 5 mg/kg infliximab, respectively, achieved PASI 75 score, compared with only 6% of patients in the placebo-group ($p < 0.001$). The high degree of response

began to decline in the 3 mg/kg group as early as week 10, whereas in the 5 mg/kg group it persisted until week 14. Five mg/kg of infliximab was proved to be the ideal dose, as showed by the higher percentage of patients achieving PASI 75 at the end of the induction regimen.

The Evaluation of Infliximab for Psoriasis Efficacy and Safety Study (EXPRESS) was a Phase III, multi-center, double-blind, placebo-controlled trial evaluating the long-term safety and efficacy of infliximab in the treatment of skin and nail disease in patients with moderate-to-severe psoriasis (BSA $\geq$ 10%, PASI $\geq$ 12%);[24] 378 patients were enrolled in a 4:1 ratio to receive either infliximab 5 mg/kg or placebo; 301 patients were allocated to infliximab 5 mg/kg and 77 to placebo. The infliximab group received intravenous infusions of infliximab 5 mg/kg at weeks 0, 2, 6 and every 8 weeks until week 46. The placebo patients were infused at weeks 0, 2, 6, 14 and 22, crossing over in a double-blind manner to infliximab 5 mg/kg at weeks 24, 26, 30 and every 8 weeks up to week 46.

By week 6, PASI 75 response was achieved by approximately two-thirds of patients receiving infliximab and PASI 90 response was achieved by approximately one third. At the end of the induction period (week 10), the above-mentioned goals were achieved by more than 75% and 50% of infliximab group patients, respectively, compared with less than 5% of the patients in the placebo group ($p < 0.0001$). These data showed a continuous increasing in the response of patients rate during the induction period; at week 10, complete clearing of skin lesions was observed in approximately a quarter of infliximab-treated patients. Also nail disease was proved to benefit from infliximab treatment (Figure 1).

By week 50, 61% and 45% of infliximab-treated patients had achieved PASI 75 and 90 responses, respectively; the percentages of patients who had achieved PASI 50, 75 and 90 were proved to be consistent with the degree of improvement shown at the end of the induction period (week 10).

The decline in PASI 75 at week 50 was not clinically significant; nevertheless, it is important to investigate why some patients present a decrease in infliximab-response from week 30 to 1 year. Possible explanations are high levels of serum infliximab concentrations, changes in serum infliximab concentrations or the presence of neutralizing antibodies. In fact, maintenance of response appeared to be related to both the level of serum infliximab concentration achieved at week 10 and the stability during treatment. In addition, maintenance of clinical response was more commonly reported when antibodies to infliximab were absent, although it must be emphasized that failure to respond to infliximab was not fully reflected by an antibody-positive status.

Therefore, in this study infliximab was proved not only to be highly effective and rapid in the onset of action, but also to result in long-term remission of skin and nail lesions.

Infliximab and other systemic anti-psoriatic treatments

Similarly to other biologics, infliximab is currently recommended by regulatory guidelines only as second-line therapy for patients complying with the following requirements: having failed to respond to conventional systemic agents and/or having become intolerant to conventional systemic therapy and/or being unable to receive conventional systemic therapy due to an increased risk of clinically relevant drug-related toxicity.[25,26] Nevertheless, there is a lack of evidence from "head-to-head" clinical trials comparing systemic biologic and non-biologic therapeutic options; however, two meta-analyses have been recently published, in which biologic drugs were compared alone and against non-biologic systemic treatments, respectively.[27,28]

Based on the PASI score and by a quantitative indirect analysis, Brimhall et al[27] compared the efficacy of alefacept, efalizumab, etanercept and infliximab for moderate-to-severe plaque psoriasis. Efficacy outcomes abstracted from this meta-analysis were 50%, 75% and 90% improvement in the PASI score (PASI 50, 75 and 90, respectively) at 10 to 14 weeks of treatment. Indirect comparison of the efficacy endpoints, all similarly compared with placebo, led to the following decreasing rank order of effectiveness: infliximab, etanercept, efalizumab and alefacept. Nevertheless, caution must be exercised in interpreting these results because of the short duration of the analyzed studies, the different methodologies and administration (schedules and routes of admission) of the four different biological agents.

Schmitt et al[28] took into account several randomized controlled trials (RCTs) of both biologic and non-biologic systemic treatments approved for moderate-to-severe psoriasis. Similarly to the previous meta-analysis, improvements in the PASI score were compared in order to determine the comparative efficacy of these systemic drugs. In all the RTCs included in this meta-analysis, biologic and non-biologic treatments were administered at the recommended therapeutic dosage and compared with placebo or with other active treatments. Moderate-to-severe plaque psoriasis was deemed on the basis of a PASI cut-off of 7. The non-biologic systemic therapeutic options analyzed were ciclosporin (2.5–5 mg/kg), methotrexate (15 mg weekly), and fumaric acid esters.

By contrast, biologic systemic agents studied by this meta-analysis were infliximab (5 mg/kg), etanercept (both 2 × 25 mg weekly and 2 × 50 mg weekly, respectively), efalizumab and adalimumab. The rate of patients with at least 75% reduction in PASI was the primary efficacy outcome. Absolute risk differences (RDs) were adopted as effectiveness measure. The authors were not able to find any head-to-head studies of different biologic treatments or of non-biologic agents; the time interval until assessing the primary efficacy ranged between 8 and 16 weeks. The most efficacious treatment found was infliximab (RD 77%, 95% CI 72%–81%), followed by adalimumab, which were significantly more effective than all the remaining interventions analyzed. These findings support the conclusions of the previous meta-analysis. Nevertheless, in a subset patients initially responding to infliximab a relapse in disease activity was recorded after 6 months of treatment, whereas etanercept was shown to be more reliable in inducing stable long-term response rates.

Based on the currently published data, among the TNF-α antagonists infliximab appears to be the fastest drug inducing disease remission, with 80% of patients achieving PASI 75 at week 10 and a sustained response among the same patients at week 24. On the other hand, the clinical response with etanercept or adalimumab administration is characterized by a slower onset and a steady increase between weeks 12 and 24, leading to an approximate rate of 50% of the etanercept-treated patients and 64% of the adalimumab-treated patients reaching a PASI 75 response at week 24.

However, it should be emphasized once again that the clinical studies included in these meta-analyses are not head-to-head trials; thus they do not fulfill the need for direct comparator trials and they must be confirmed and strengthened by pragmatic head-to-head RCTs, lasting at least 2 years and comparing different biologic drugs both with each other and with conventional systemic treatments for psoriasis.

Safety, tolerability and management of infusion reactions

The overall safety profile of infliximab seems to be similar in all its indications. It cannot be excluded, however, that certain safety aspects (such as the risk for skin cancer and liver disease) differ with regard to patients with plaque-type psoriasis due to their past medical history, including previous exposure to UV phototherapy, methotrexate or other medications. At present, there is a lack of sufficient long-term data about the safety of infliximab in patients with plaque psoriasis. For the safety of this chimeric biologic, key points that must be included are infusion/injection reactions and infections, including rare but important opportunistic infections.

As for other foreign protein-derived treatments, the intravenous administration of infliximab is also at risk of causing infusion reactions, which can be classified as acute reactions, occurring during the infusion or in the first 24 hours afterwards, or delayed reactions, occurring between 24 hours and 14 days after the infusion (for the most part after 5–7 days).[29] Acute infusion reactions are usually graded as mild, moderate or severe, based on patients' signs and symptoms,[29–31] and appeared to be the most frequent reason for discontinuation of therapy in clinical trials (2.8% discontinuation rate in all clinical trials). In the EXPRESS clinical trial, infusion reactions were observed in about 3% to 7% of infusions with infliximab compared with 1% to 2% of infusions with placebo.[24] Most infusion reactions were mild (flushing, dizziness, headache, sweating, palpitations or nausea) to moderate (chest tightness, shortness of breath, hypo/hypertension, raised temperature or urticaria), whereas severe infusion reactions (a change in blood pressure of more than 40 mmHg, wheezing, stridor, severe fever with rigors) were rarely reported. Among 935 patients in clinical trials, 3% had non-specific fever and chills, and less than 1% of infusions were serious, including anaphylaxis and hypotension.[32] Acute infusion reactions to infliximab often develop with symptoms suggestive of anaphylactic reactions (systemic reactions due to the massive IgE-mediated release of mast cell products, such as histamine, triptase or cytokines, also known as type I hypersensitivity reactions);[33] however recent evidence seems to prove that most of the anaphylactic-like reactions to infliximab are anaphylactoid rather than true type I hypersensitivity reactions,[29,30,34,35] being clinically similar to the latter but having a different pathogenesis (mast cells are directly degranulated and activated, without IgE playing any role). As for delayed infusion reactions to infliximab, they clinical resemble mild serum sickness (rash, fever and polyarthralgias/polyarthritis), even if typical laboratory findings have not been identified.[30,36] Interestingly, the incidence of mild to moderate infusion reactions has been proven to be relevantly increased if case of infliximab administration leading to the development of human antichimeric antibodies versus infliximab, also known as ATI;[24,29] ATI occurs in 7% to 61% of patients suffering from psoriasis, RA and Crohn's disease;[37] Baert et al[38] showed in a retrospective cohort study that a high risk of infusion reactions can be predicted by ATI serum concentrations of 8 μg/mL or higher. The risk of developing ATI appears to be linked to both the infusion schedule and the co-administration

of immunosuppressants. Despite the lack of good comparative clinical studies, there is some evidence that the formation of ATI is less likely to develop by loading the infliximab therapy with three infusions, respectively at weeks 0, 2 and 6, instead of only one initial infusion,[36] and by maintenance treatment (an infusion every 8 weeks) instead of on-demand infliximab administration.[39] The combination of infliximab and methotrexate seems to be particularly interesting; based on previous experiences in Crohn's disease and RA,[40–42] the combination with methotrexate, especially if the regimen is continued for more than 4 months, significantly reduces the immunogenicity of infliximab and, as a consequence, the risk of ATI formation and infusion reactions. However in this case the possibility of immunosuppression is higher. It is also important to emphasize that there is no solid evidence about the efficacy of premedication (consisting of paracetamol, anthistamines or steroids given before the infusion) either in primary or secondary prophylaxis against infusion reactions,[43–45] although it is routinely administered for both purposes and it might lower the severity of a potential infusion reaction; consequently the additional benefits deriving from the routine premedication should be weighed against the chance of potential side-effects, even if small. In case of mild or moderate acute infusion reaction, it is recommended to slow down the infusion or even to interrupt it, to infuse physiologic saline, to treat with antihistamines and paracetamol, then to restart the infliximab infusion at an initially reduced rate. A delayed infusion reaction should be treated by administrating antihistamines and, if indicated by the severity of the situation, steroids. Mild to moderate reactions should not induce the physician to interrupt the infliximab treatment, whereas in case of serious reactions it is suggested that the pros and the cons of the therapy should be evaluated.

In order to reduce the risk of a new reaction, besides a stronger premedication, other available options are: 1) modifying the dosage, 2) reducing the rate of the infusion in case of a previous acute reaction, 3) reducing the interval between infusions in case of a previous delayed reaction,[29] 4) adding an immunosuppressant such as methotrexate, 5) desensitizing procedure (an extreme solution which should be adopted only if infliximab treatment is to be continued despite a severe reaction).[38]

Infections

As an immunosuppressant, infliximab can reduce resistance to infection, because TNF is a pivotal cytokine in the host defense, especially against certain infective pathogens. Infections are the most common adverse events reported in literature related to TNF-α antagonists. There seems to be an increased risk associated with TNF antagonist treatment for severe and soft tissue infections, for bacterial intracellular infections, and for granulomatous infections.[46] Tuberculosis is the most frequent granulomatous infection occurring under anti-TNF-α treatment; TNF-α is essential for tubercular granuloma development and disease containment, so that TNF inhibition might lead to reactivation of latent tuberculosis infection (LTBI). Therefore, potential recipients of TNF antagonists should be rigorously screened for tuberculosis (TB), with a detailed medical history, questioning about potential TB exposure including recent travel assessment for symptoms such as cough and weight loss, purified protein derivative (PPD) skin testing and a chest radiograph. In case of a positive PPD test associated with a negative chest X-ray, infliximab could be administered in association with a concomitant antitubercular chemoprophylaxis (isoniazid prescribed for 6–9 months).[47] However, this clinical approach does not completely avert the chance of a tubercular reactivation.[48] Interferon assay (QFT-G), being highly specific and sensitive in diagnosing LTBI,[49] should be employed in parallel with conventional procedures, assuming LTBI in case of a positive result of any of the aforementioned assays. For the same reason, before starting the infliximab treatment every patient ought to be tested for hepatitis and HIV serologic markers. Besides the tubercular risk, other rare and/or opportunistic infections have been reported in association with infliximab therapy, such as pulmonary actinomycosis,[50] *Listeria monocytogenes* and *Plasmodium falciparum* sepsis,[51,52] latent visceral *Leishmania* reactivation,[53] cryptococcal meningitis and life-threatening histoplasmosis.[54,55] As with other immunosuppressive drugs, infliximab should not be given to patients with active infections. The value of screening measures has been highlighted by the reduction of reported TB cases in patients receiving infliximab after the regular adoption of educational programs and screening for TB, although the role of screening is more uncertain in relation to opportunistic pathogens' prevention.[46]

Infliximab, quality of life and nail involvement

Psoriasis influences significantly the health-related quality of life (HRQoL) issues, including the physical, psychological and social facets of the patient's life.[56,57] For this reason, as proved by different studies, the treatment with infliximab is effective even on patient QoL. Feldman et al[58] in the

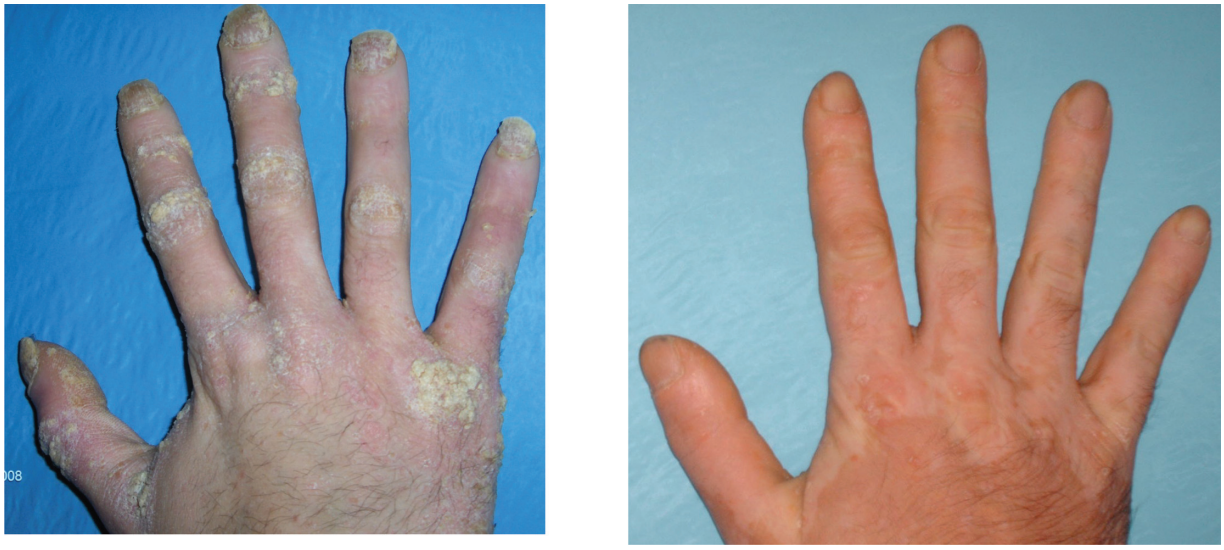

Figure 1 Complete clinical response of plaque type psoriasis with nail involvement after 3 infusions of infliximab.

EXPRESS II study involving 835 patients with moderate-to severe plaque psoriasis, showed that infliximab is associated with a dramatic improvement of disease severity (PASI) and HRQoL (Dermatology Life Quality Index, DLQI; 36-item Short-Form Health Survey, SF-36). In particular patients treated with infliximab gained significant improvements in both non-specific HRQoL (evaluated by SF-36, PCS and MCS) and disease-specific HRQoL (measured by DLQI), compared with placebo. Infliximab significantly improved HRQoL and related comorbidities such as depression and anxiety, underlying that a comprehensive assessment of treatment efficacy against psoriasis must include the evaluation not only of the severity of skin lesions but also of social and psychological morbidities.[59]

In this context 20% to 55% of patients with psoriasis suffer from nail psoriasis.[60] Nail involvement (usually measured in clinical trials by the nail psoriasis severity index, NAPSI score) is a relevant source of distress due to its chronic course (characterized by flare-ups and remissions), the localization of the lesions (affected fingernails are visible during the whole year, disfigured toenails torment female patients during summertime) and the predisposition to bacterial or mycotic infections in case of nail dystrophy; and the pain represents a serious obstacle to daily activities.[61] Nail psoriasis has a great impact on HRQoL, increasing the depression and anxiety scores among PsA.[61] Moreover, many authors have found a relationship between nail disease and PsA:[62–65] there is an increased prevalence of nail involvement among patients with PsA. Gladman et al[66] proposed that this feature is the only one clinically able to identify psoriatic patients prone to develop PsA in the near future. Since the extensor tendon enthesis forms an integral supporting structure for the nail,[67] it has been hypothesized that the anatomical proximity could explain the association between distal interphalangeal involvement (DIP), enthesopathy and nail dystrophy in PsA.[68] In this way nail psoriasis could represent a pathogenetic connection between skin and joint involvement.[69] However, this assumption has been denied by other clinical studies, which have failed to find a significant association between DIP and nail involvement;[70,71] nevertheless, in patients without PsA, nail disease is associated with bone involvement of the distal phalange (valued as erosion and/or osteitis as seen by means of hands and feet X-ray), and the severities of these conditions appear to be correlated.[72]

Therapy of psoriatic nails represents a challenge for dermatologists. In psoriatic patients with nail involvement, infliximab proved to be effective in significantly ameliorating the NAPSI score after three infusions, leading often to complete remission by the next one/two infusions.[24,61,72] The efficacy is directed against both matrix and nail bed signs, and no significant difference has been detected between patients with or without PsA. In case of nail psoriasis, systemic therapy should be adopted only if there is extensive skin and/or joints involvement or if there is an extremely severe condition such as pustular psoriasis.[73,74]

Infliximab and psoriatic arthritis

PsA is a chronic inflammatory arthropathy characterized by different clinical forms of joint disease ranging from mild

synovitis to severe erosive arthritis. The latter occurs in 40% to 60% of PsA patients, showing a progressive course from the first year of diagnosis.[75,76]

Infliximab has been proved to be effective in the treatment of PsA. FDA and EMEA have approved its use in active and progressive PsA. In the placebo-controlled randomized trials relating to the efficacy of infliximab in PsA, achievement of the ACR20 was established as the primary end point. In order to achieve an ACR20 response, the following clinical and laboratory findings were required: at least a 20% reduction in the number of tender joint count, at least a 20% reduction in the swollen joint count, and at least a 20% improvement in at least three of the following assessments: patient pain assessment, patient global assessment, physician global assessment, patient self-assessed disability, and acute phase reactants (C-reactive protein or erythrocyte sedimentation rate).[77] In the phase II and phase III controlled clinical trials evaluating the administration of infliximab in patients with PsA, the rate of infliximab-treated patients achieving an ACR20 response after 12 to 16 weeks was significantly higher than the rate in the placebo group; in the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) and IMPACT 2 trials, 65.4% (IMPACT) and 58% (IMPACT 2) of patients with PsA receiving infliximab (5 mg/kg at weeks 0, 2, and 6, then every 8 weeks, 1 concomitant DMARD [IMPACT] or concomitant methotrexate [IMPACT2] allowed) achieved an ACR20 response at week 16 and at week 14, respectively (placebo, 10% [IMPACT] and 16% [IMPACT 2]).[78,79] At the same time points, an ACR70 response was achieved by 15% and 28% of patients in the infliximab-treated group (placebo, 0% and 1%, respectively). Of note, the clinical response to infliximab was sustained throughout a radiographic assessment showing the inhibition of the disease progression and the potential property of preventing irreversible joint impairment.[80]

The management of long-term treatment

Currently no definite guidelines are available with regard to the long-term management of infliximab therapy. However this information is crucial because psoriasis a chronic disease and as a consequence specific treatments are likely to have to be continued for a long time. Despite the lack of well established data-based clinical investigations into the long-term administration of infliximab, a dermatology expert panel recently reached a consensus in this issue, explaining key decision points about long-term moderate-to-severe psoriasis management and long-term infliximab therapy.[81] In relation to the initial level of efficacy, the consensus of the panel was that an improvement in symptoms should be at least 75%. After 12 weeks (induction period) of treatment, infliximab should be continued as long as the patient has achieved at least PASI 50. If the patient fails to achieve PASI 50 after 6 months, this may be considered a "non-response" and patients should be switched to another treatment.

During the long-term treatment with infliximab, a slight decrease (10%–20%) in PASI score can be observed. This trend does not indicate that the therapy is not successful any more, as long as the absolute level of PASI and improvement in DLQI remain acceptable. Until the consensus statements are corroborated by robust clinical data, these recommendations provide at this time reliable guidelines about how to manage infliximab treatment in the long term.

Costs

One of the main limitations to the use of infliximab as well as other biologics as first-line anti-psoriatic agents is their cost. For this reason in Europe, biologics can be prescribed only in patients unresponsive or with contraindication to conventional treatments.

The pharmaceutical total cost for infliximab for moderate-to-severe psoriasis after 1 year is €15,162.64. A recent Italian study (unpublished) evaluating the cost-effectiveness of infliximab compared with the others biologic agents for the treatment of psoriasis showed a higher efficacy both in terms of PASI and DLQI scores of infliximab when compared to efalizumab, adalimumab and etanercept.

Conclusions

This review demonstrated a high degree of clinical response to infliximab in patients with moderate-to-severe plaque psoriasis. The results showed a rapid response in onset and persistence over time for the majority of patients, especially for those who received regular infusions of 5 mg/kg every 8 weeks. Improvement in PASI was paralleled by improvement in PGA score and QoL, as assessed by DLQI and SF-36 scores. This anti-TNF-α agent was shown to be effective in the treatment of nail psoriasis, although the latter alone cannot be considered an indication for infliximab. If nail psoriasis is recognized as an early sign of joint involvement, the current guidelines will be probably appropriately addressed.

Infliximab has an encouraging safety profile, especially as long as physicians are watchful in preventing and early diagnosing infections and infusion reactions. The long-term treatment should be managed based on the sustained achievable

efficacy and on the specific demands of individual patients, although further clinical studies are needed to investigate this issue and to produce definite guidelines.

Expert opinion

At the University of Rome Tor Vergata, we have been using infliximab for 7 years and we have treated more than 250 patients. Infliximab has been shown to have a rapid onset of action maintaining a sustained efficacy for up to 4 to 5 years of continuous therapy in terms of PASI 75 and PASI 90. Temporary reductions in efficacy have been observed after the 6th year. When a loss of response to infliximab is observed, we suggest: 1) waiting and monitoring the patient for the next two infusions; 2) if the patient shows a persistent loss of efficacy, a drug such as methotrexate or ciclosporin could be combined for a short period until efficacy is regained. In other cases reduction of the infliximab infusion interval from 8 to 6 weeks or 4 weeks can be considered.

In our daily practice the choice among infliximab and other biologics is made according to patients and their disease features. Patients with significant psychological involvement or with more severe disease are treated with infliximab since this anti-TNF-α agent is characterized by a more rapid clinical response. In contrast patients preferring a subcutaneous and intermittent therapy are treated with the other anti-TNF-α agents.

To monitor drug safety and the risk of opportunistic infections, we suggest chest radiography once a year, the interferon assay for the increased risk of TB twice a year and blood exams at every infusion.

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