Infliximab in the treatment of plaque psoriasis

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Plaque psoriasis is a chronic and immune-mediated skin disease that affects approximately 1–3% of the Caucasian population. TNF-α is a proinflammatory cytokine that plays a critical role in the pathogenesis of psoriasis. Infliximab is a chimeric anti-TNF-α monoclonal antibody with high affinity for soluble and cell-surface transmembrane TNF-α. Results from Phase II and III trials and long-term studies with continuous and intermittent maintenance regimens indicate that regular infusions of infliximab (5 mg/kg) are highly effective, with a rapid onset of response, safety and improvement in quality of life. Infliximab is generally well tolerated, but may be associated with adverse events such as infections, malignancies or loss of response due to the development of neutralizing antibodies.

Psoriasis is a lifelong, chronic and immune-mediated skin disease that is characterized by erythematous scaly plaques. Psoriasis affects approximately 1–3% of the Caucasian population and, in the USA, the prevalence has been estimated at 2.2–2.6% [1].

The most common clinical variant is plaque psoriasis, which occurs in more than 80% of affected patients [2]. Erythematous scaly plaques, round or oval and variable in size, typically affect the scalp, lower back, intergluteal cleft, umbilical area, elbows and knees. The number of lesions can vary from few (localized psoriasis) to several confluent elements, which can affect the whole cutaneous surface (widespread psoriasis). Pitted fingernails, subungual hyperkeratosis or onychodystrophy occur in 50% of patients and could aid in diagnosis when other characteristic clinical features are lacking [3]. Up to 40% of psoriasis patients develop an inflammatory deforming arthritis termed psoriatic arthritis [4].

T lymphocytes and dendritic antigen-presenting cells (APCs) have been considered to be of major importance in the immunopathogenesis of psoriasis, and current evidence suggests that epidermal changes are caused by the actions of these cells in skin lesions [5,6].

The role of T cells in psoriatic plaques has been confirmed by the presence of activated T cells in psoriatic plaques. Most of the T lymphocytes that localize to the dermis are $CD4^+$ helper cells, while those that migrate to the epidermis are predominantly $CD8^+$ cytotoxic T cells. Activated T cells in psoriatic skin produce Th1-type cytokines, including IL-2, IL-1, IFN-γ and TNF-α [7]. The most important evidence that psoriasis is an immune-mediated disease comes from the finding that psoriasis can be reversed with a lymphocyte-selective toxin (DAB389IL-2). Effector cells of innate immunity are also involved in the pathogenesis of psoriasis; they include neutrophils, plasmacitoid dendritic cells (DCs) and $C11c^+$ DCs. Activated DCs producing IL-23 and inducible nitric oxide synthase (iNOS) are present in psoriasis plaques. Plasmacytoid DCs produce high levels of IFN-α, while $CD11c^+$ DCs express high levels of TNF-α [1,8].

Unmet needs in the treatment of psoriasis

Treatment for psoriasis includes monotherapy and combination therapies. Several systemic treatments are available for the treatment of moderate-to-severe plaque psoriasis, including UVB phototherapy, psoralen plus UVA, retinoids, cyclosporine and methotrexate. While these therapies exhibit efficacy in the treatment of psoriasis, they also are associated with specific toxicities and tolerability problems, which may limit their use in some patients. Cyclosporine is associated with hypertension and renal toxicity, while methotrexate is associated with abnormal liver function, teratogenicity and bone marrow failure. Clearly, there is a need for safe chronic therapy for patients with moderate-to-severe disease, who require long-term treatments. In addition, patients have indicated that they are not satisfied with current treatments: only 26% of patients appear to be satisfied with their current therapy, and 44% of patients prefer systemic therapy to topical treatment, indicating that new systemic drugs are

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needed [9]. The majority of patients with moderate psoriasis or mild and localized psoriasis, for which topical therapies remain the mainstay of treatment, are frustrated by the ineffectiveness of the medications, the time required to treat their disease and the inconvenience of topical treatments [10,11]. For this reason, these patients prefer systemic therapy to topical regimens.

The realization that psoriasis is an immune system dysfunction rather than a primary skin disorder has led to the development of a new generation of therapies for psoriasis that target the immune system. Many of these medications are termed biologic therapies because they are protein drugs produced in living organisms. Biologicals are a set of bioengineered proteins used to modify immune reactions. They are designed to modify defined pathophysiological pathways that regulate pivotal immunological processes, such as lymphocyte activation, interaction with APCs and endothelial cells (adhesion and migration), and production and action of cytokines and chemokines. They interfere with specific components of the autoimmune response and, in contrast to general immunosuppressants, do not affect the entire immune system or have significant end-organ toxicity. Antibodies, fusion proteins and recombinant cytokines are examples of such biologicals.

Infliximab & TNF-α

Infliximab is a biologic therapy developed for the treatment of chronic inflammatory diseases mediated by TNF-α, and is approved in the USA and Europe for the treatment of gastroenterological and rheumatological diseases, namely Crohn's disease, ulcerative colitis, psoriatic arthritis, ankylosing spondylitis and rheumatoid arthritis. Infliximab has recently been approved by the US FDA and European Medicines Agency (EMEA) for the treatment of plaque psoriasis. The approval was based on data obtained from previous clinical trials.

Infliximab is a chimeric anti-TNF-α monoclonal IgG_1 antibody with high affinity and avidity for soluble and cell-surface transmembrane forms of TNF-α. Detection of increased levels of TNF-α in psoriatic plaque suggests it has a role in keratinocyte proliferation, expression of adhesion molecules on keratinocytes and endothelial cells, cell trafficking, and enhancement of neutrophil functions [12]. In addition, increased serum TNF-α levels are linked with a higher disease activity, and are reduced by effective therapies. By blocking both soluble and cell-surface transmembrane TNF-α, infliximab induces a rapid decrease of epidermal T-cell infiltration, downregulates adhesion molecule expression and normalizes keratinocyte proliferation [13].

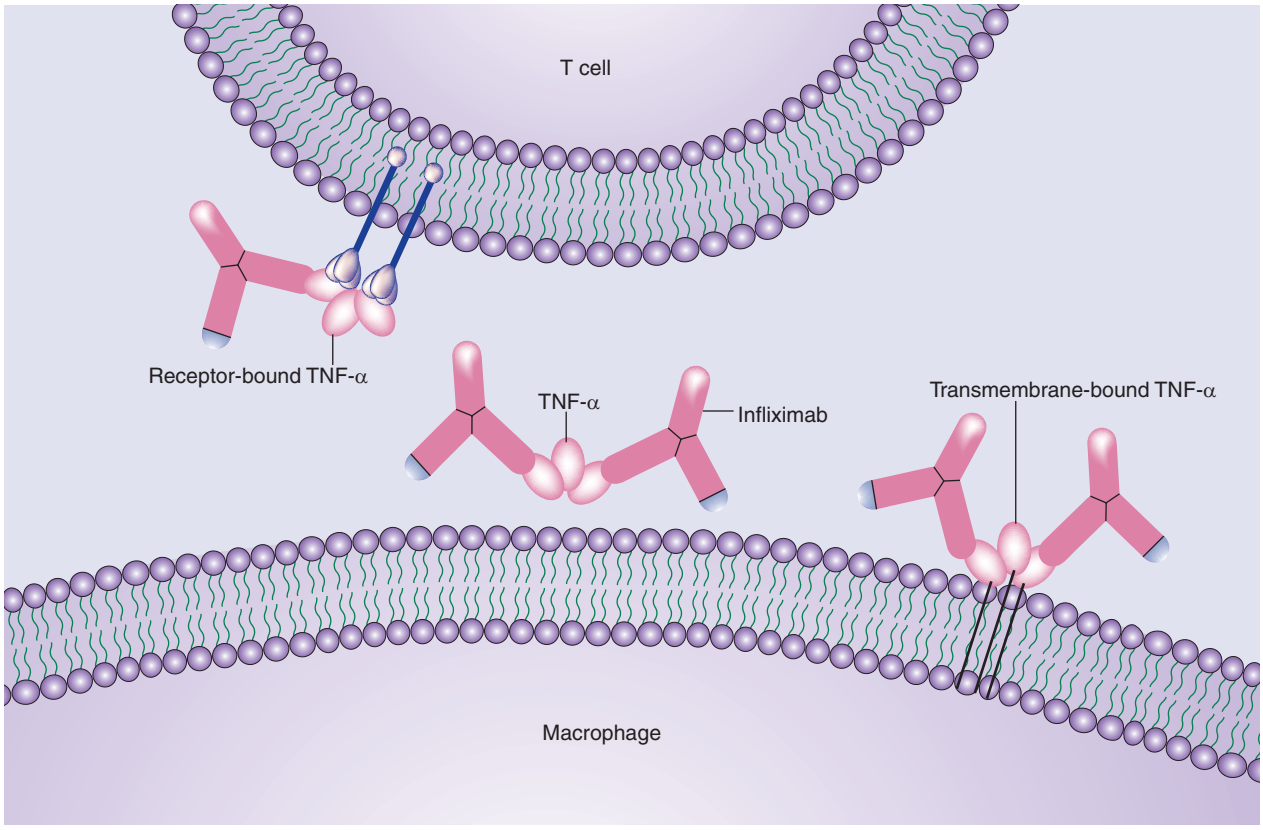
TNF-α is a proinflammatory cytokine produced by many different cell types, including activated T cells, keratinocytes, Langerhans' cells and other dendritic APCs. TNF-α is inactive as a monomer, but forms active trimers, composed of three monomers. It exerts its biological activity by binding to specific high-affinity cell-surface receptors – p75 and p55. Both receptors can be shed from the cell surface and give rise to soluble receptors, which can compete with the cell-bound receptors for binding to TNF-α. This cytokine has numerous effects on the immune response, driving activation and recruitment of other inflammatory cells, amplifying production of IL-1, IL-6 and IL-8, and activating nuclear transcription factors such as NF-κB to propagate and maintain an inflammatory response [14]. In psoriasis, level of both TNF-α and TNF-α receptors are higher and more widely expressed in lesional skin compared with normal skin. TNF-α induces Langerhans' cell maturation, creating more efficient APCs with increased T-cell costimulatory molecules and inducing their migration from the skin to the lymph nodes, where antigen presentation and T-cell activation take place. Moreover TNF-α leads to the production of transforming growth factor (TGF)-α, which may drive keratinocyte proliferation in psoriasis [15].

Pharmacological profile

Infliximab has a molecular weight of 149,100 Da and comprises a mouse variable region and a human IgG1/α constant region [16]. Each infliximab molecule can bind two TNF-α molecules and also to TNF-α that is already bound to the TNF-receptor. Up to three infliximab molecules can bind and block a single trimer of TNF-α (**Figure 1**). By binding to soluble and transmembrane TNF-α molecules in the plasma and diseased tissue, infliximab directly neutralizes TNF-α and retards or prevents the monomeric association that forms the biologically active trimer [13]. Infliximab-bound TNF-α cannot bind to or activate the TNF-α receptor on target cells. In the skin, TNF receptor-bearing cells include keratinocytes, Langerhans' cells, T cells, natural killer (NK) cells and endothelial cells.

The recommended dose is an infusion of 5 mg/kg followed by additional doses at 2 and 6 weeks after the first infusion and then every 8 weeks thereafter. It is administered to patients

Figure 1. Structure and mechanism of action of infliximab.



via intravenous infusion over 2–3 h. In general, higher infliximab blood levels are associated with higher clinical efficacy. Patients with undetectable serum infliximab concentrations (<0.1 µg/ml) are less likely to maintain response. The median elimination half-life for infliximab is 7.62 days (interquartile range: 6.62–10.15 days) for the 5-mg/kg dose [13].

Clinical efficacy

In clinical trials involving patients with moderate-to-severe psoriasis, infliximab infusions were given at variable dosages of 3, 5 and 10 mg/kg of body weight (**Table 1**). These studies showed rapid improvement from baseline and infliximab was generally well tolerated [17–26]. Inclusive eligibility criteria were: age greater than 18 years, moderate-to-severe plaque-type psoriasis, and no response or ineligibility to conventional current systemic treatments. Exclusion criteria were: drug-induced psoriasis, live vaccinations, history of chronic or recurrent serious infectious disease or opportunistic infection, evidence of internal malignancies or serious infections within 3 months prior to the first infusion, signs or symptoms of systemic lupus erythematosus, demyelinating diseases, lymphoproliferative diseases or noncutaneous malignancies within the previous 5 years, and serious congestive heart failure.

Patients could not use any other treatment for psoriasis during the entire duration of the studies, except for nonmedicated emollients and nonprescription tar or salicylic shampoos. They stopped taking systemic therapy (UVB, PUVA, cyclosporine, methotrexate or acitretin) at least 4 weeks before, and stopped using topical therapy at least 2 weeks before receiving the first dose of study medication.

TNF-α plays an essential role in host defence against tuberculosis, including granuloma formation and containment of disease. Reactivation of tubercolosis is a risk with inhibition of TNF-α; for this reason, all patients should be screened for latent tubercolosis with history, physical examination and purified protein derivative (PPD) skin tests. Patients with a positive PPD test, but negative chest x-ray, may receive infliximab infusions after taking the antitubercular treatment prescribed for up to 6–9 months.

The overall utility and benefit of antipsoriatic therapies were commonly measured by the physician global assessment (PGA), body surface

area (BSA), the percentage of patients achieving at least 50 and 75% improvement in psoriasis area and severity index (PASI 50 and PASI 75, respectively) and the impact on quality of life (QoL) using the dermatology life-quality index (DLQI).

Phase II studies

The first Phase II study was designed to assess the safety and efficacy of infliximab in 33 patients with plaque psoriasis in comparison with placebo, with two doses of infliximab (5 and 10 mg/kg) given at weeks 0, 2 and 6 [17]. Patients who received infliximab had a higher degree of clinical benefit and a more rapid time to response than patients who received placebo. Most responders (82%) had excellent or clear rating on the PGA and achieved the PASI 75. This study did not show a clinically significant difference between the 5- and 10-mg/kg doses of infliximab in terms of efficacy. The mean percentage improvements in PASI scores were significantly higher ($p < 0.0003$) among infliximab-treated patients by as early as week 2. In both of the infliximab treatment groups, the median time to response was 4 weeks. According to the safety and efficacy profile, the comparison between 5 and 10 mg/kg suggested that a regimen with 5 mg/kg was superior. The dose was further investigated by a comparison between 3 and 5 mg/kg.

The second published Phase II study was a multicenter, double-blind, placebo-controlled trial; 249 patients with severe plaque psoriasis were randomly assigned to receive intravenous infusions of infliximab or placebo [18]. The aim of this trial was to evaluate the efficacy and safety of a three-dose induction regimen of infliximab in patients with greater than 10% BSA. The trial was also designed to test whether infliximab could safely be readministered to patients 20 weeks after completion of the induction regimen. Eligible patients were randomly assigned in a 1:2:2 ratio to intravenous infusions of placebo or infliximab (3 and 5 mg/kg, respectively) and were treated at weeks 0, 2 and 6. Of patients in the infliximab treatment groups, 80% completed the 30-week study period compared with only 31% of patients receiving placebo. Response was evident after the first infusion of infliximab. At week 2, 34 and 40% of patients in the 3- and 5-mg/kg infliximab-treatment groups, respectively, achieved PASI 50 compared with 4% of patients in the placebo group. A total of 72% of patients receiving 3 mg/kg and 88% receiving 5 mg/kg achieved the PASI 75 score from baseline at week 10, compared with only 6% of patients receiving placebo. The higher percentage of patients achieving a PASI 75 confirmed 5 mg/kg as the best dose of infliximab. Infliximab treatment also resulted in substantial improvement in QoL, as measured by DLQI.

Table 1. Published clinical trials on the treatment of plaque psoriasis with infliximab as monotherapy.

Authors	Phase of study	Patients (n)	Dose	PASI 75 at week 10 (%)	Ref.
Chaudhari *et al.* (2001)	Phase II	33	5 mg/kg 10 mg/kg Placebo	82 73 18	[17]
Gottlieb *et al.* (2003)	Phase II	249	3 mg/kg 5 mg/kg Placebo	72 88 6	[18]
Reich *et al.* (2005)	Phase III	378	5 mg/kg Placebo	80 3	[19]
Kalb and Gurske (2005)	Retrospective	52	5 mg/kg	88*	[20]
Smith *et al.* (2006)	Open label	23	5 mg/kg	77	[21]
Ahmad and Rogers (2006)	Retrospective	12	5 mg/kg	66*	[22]
Menter *et al.* (2007)	Phase III	835	3 mg/kg 5 mg/kg Placebo	70.3 75.5 1.9	[26]

**Physician global assessment excellent.*
PASI 75: Percentage of patients achieving at least 75% improvement in psoriasas area and severity index.

Phase III studies

In the Evaluation of Infliximab for Psoriasis Efficacy and Safety Study (EXPRESS) Phase III study, 378 adult patients were enrolled in a 4:1 ratio to receive either infliximab 5 mg/kg or placebo [19]. The infliximab group received intravenous infusions of infliximab 5 mg/kg at weeks 0, 2 and 6, and then every 8 weeks until week 46. The placebo group 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 and 30, and then every 8 weeks up to week 46.

Of the 378 enrolled patients, 77 were allocated to placebo and 301 to infliximab 5 mg/kg. Approximately two-thirds of patients achieved a PASI 75 response and approximately a third achieved a PASI 90 response by week 6; the proportions of patients continued to increase, with more than three-quarters achieving PASI 75 and half achieving PASI 90 responses at the end of the induction period (week 10). Complete clearing of psoriasis at week 10 was reported in approximately 25% of patients.

In this study, a significantly greater improvement of nail psoriasis was also observed, as assessed by nail psoriasis severity index, in infliximab-treated compared with placebo-treated patients. At week 10, there was a 26% improvement of nail psoriasis in the infliximab-treated group, whereas in the placebo group no improvement was observed.

Maintenance of therapeutic response seemed to be related to the achievement of stable serum-infliximab concentrations and was more common in patients who were negative for antibodies to infliximab than in antibody-positive patients.

At 6 months, based on prespecified analyses, the proportions of patients achieving PASI 50, 75 and 90 were consistent with the improvements achieved at week 10 after the induction regimen, and most infliximab-treated patients achieved PASI 75 at week 50.

As psoriasis is a chronic disease that usually needs long-term treatment, understanding why some patients lost response from week 30 to 1 year is important. This finding can be attributed, in part, to patients who discontinued treatment but continued to be followed up for safety reasons. Other possible explanations for this loss in PASI 75 response include changes in serum infliximab concentrations or the presence of neutralizing antibodies.

Infliximab & psoriatic arthritis

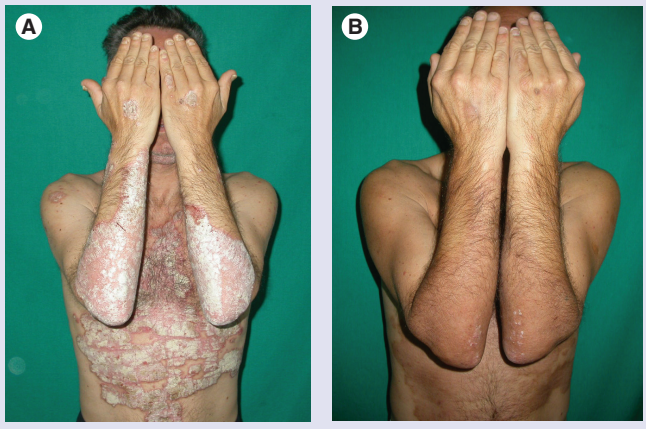
Data from several published studies document that infliximab provides significant and dramatic improvement of psoriatic arthritis. Although this review focuses on psoriasis vulgaris, studies performed on psoriatic arthritis will be mentioned. Results from the first double-blind trial in 104 patients with psoriatic arthritis (IMPACT) confirmed the efficacy of infliximab in this condition [27]. Similarly, the IMPACT 2 trial showed the efficacy and safety of infliximab in a larger group of patients with active psoriatic arthritis [28]. Infliximab 5 mg/kg was administered at weeks 0, 2, 6 and every 8 weeks thereafter up to 24 weeks. The American College of Rheumatology (ACR) criteria response was evident as early as week 2 and responses were maintained throughout the study. A significant higher proportion of patients treated with infliximab achieved the predefined end points (specifically, ACR 50 and ACR 70) at week 14 and week 24 compared with patients treated with placebo. In addition to the clinical efficacy evaluated by the standard indices of joint and skin disease, this study showed a significant improvement in QoL.

Safety & tolerability

The most common adverse events reported in the aforementioned studies were related to infusion reactions, which are defined as any adverse events occurring during 1 h of administration. In the EXPRESS study, infusion reactions were reported in the 3% of treated patients versus 2% of the placebo group. In the first Phase II studies, headache was the only adverse event that occurred in a higher proportion of infliximab-treated patients than in placebo controls. In the second Phase II study, infusion reactions were reported in 18 and 22% of patients in the infliximab (3 and 5 mg/kg) groups compared with 2% in the placebo group. The most common reactions were chills, headache, flushing, nausea, dyspnea, injection-site infiltrations and high blood pressure. Interestingly, in the randomized Phase III study of continuous (every 8 weeks) versus intermittent (as needed) infliximab regimens, the infusion reactions occurred more frequently in the 3-mg/kg group (11.5%) than in the 5-mg/kg group (9.6%). Moreover, these adverse events were more common in the as-needed group than in the every-8-weeks group.

Sepsis, pyelonephritis, diverticulitis, cholecystitis, cholelithiasis, squamous cell carcinoma, drug-induced psoriasis, autoimmune

Figure 2. Baseline of a 35-year-old man (A) before treatment with infliximab and (B) at week 10 after treatment.



hepatitis, fatal liver toxicity and lupus or lupus-like syndrome, were reported in less than 1% of patients. Pulmonary infections and, in particular, the reactivation of tuberculosis is associated with inhibition of TNF-α. For this reason, screening for tuberculosis is indicated prior to initiating therapy with infliximab.

In many studies, a positive antinuclear antibody titer, as well as antibodies to infliximab, was observed at the final assessment, which were not present at baseline. Increases in aminotransferase concentrations, which occurred more commonly in alanine aminotransferase than aspartate aminotransferase, were also observed.

Cost

The price of a 100-mg vial in the USA is US$52,775. A single dose of 5 mg/kg infliximab for a 70-kg patient would cost US$2111, and the annual cost would be US$19,000. In Europe, the cost of a 100-mg vial of infliximab is €46,627. Therefore, a single dose for a 70 kg patient would be €1865.08 and the annual cost would reach €16,785. However, these costs do not include start-up costs for the administration of the drug.

Conclusion

Psoriasis is a persistent, disfiguring and stigmatizing disease that has an enormous physical, functional and psychosocial impact on patients. As psoriasis is a lifelong, chronic and immune-mediated skin disease it is necessary to find a lifetime treatment, and traditional therapies, although effective, have numerous shortcomings. Many systemic therapies are associated with cumulative toxicities, such as end-organ damage, cancer, renal and liver compromise, thus limiting their use.

Among the biologicals, the rapid clearing of psoriatic plaques and the substantial improvement in QoL allows us to consider infliximab a valid and effective drug. The response to infliximab is rapid in onset (**Figure 2**) and can persist over time, especially if the therapy is received with regular infusions of 5 mg/kg every 8 weeks [26] and in association with methotrexate.

Compared with other anti-TNF-α compounds, infliximab is characterized by a rapid onset, and most patients experience significant improvement after only one or two infusions. By contrast, infusion reactions, side effects and the 2–3 h intravenous infusion are considered the inconveniences of this drug (**Table 2**).

Expert commentary & future perspective

In the last 5 years, there has been a significant effort to devise newer medications for psoriasis that may be used for more prolonged periods with an improved safety profile. The realization that psoriasis is an immune system dysfunction

Table 2. Clinical profile of approved anti-TNF-α drugs and their costs.

Drug	Efficacy	Safety	Convenience	Annual cost (US$)	Assumption
Infliximab*	++++	+	+	19,000	Four vials for eight infusions
Etanercept*	++	++++	++++	21,125	52 doses of 50 mg for 1 year
Adalimumab‡	+++	+++	++++	18,400	26 doses for 1 year

FDA and EMEA approved for psoriatic arthritis and psoriasis vulgaris.

‡FDA and EMEA approved for psoriatic arthritis.

rather than a primary keratinocyte skin disorder has led to the development of a new generation of therapies for psoriasis that target the immune system. Biologics have revolutionized the treatment of rheumatoid arthritis and Crohn's disease and are impacting significantly on the management of psoriasis. Similarly to infliximab, other biologics, such as etanercept, adalimumab, alefacept and efalizumab, have shown promise in their ability to maintain long-term clearance of psoriasis. Currently, infliximab is indicated for cases of moderate-to-severe psoriasis, psoriatic arthritis and for patients who are unresponsive to or ineligible for conventional systemic therapies.

The advantage of biologics is that they may be less toxic than other conventional or traditional systemic therapies when administered in the long term. In addition, biologics are nonteratogenic and do not have the multiple drug-interaction liabilities that many of the traditional systemic therapies have.

There is a considerable knowledge regarding the safety of anti-TNF-α therapies, as they have been used continuously over a number of years for patients with rheumatoid arthritis and Crohn's disease.

Furthermore, these drugs can also be used in combination with other drugs, such as acitretin or methotrexate, when the response to disease-modifying agents is inadequate. Infliximab's strengths are its rapid induction of clearance, high proportion of patients achieving PASI 75 after induction therapy and the greater than 800,000 patient history of use. The loss of response over time, infusion reactions, and the inconvenience and cost of intravenous infusion therapy may limit its use in some practices.

In rheumatoid arthritis and psoriatic arthritis, early diagnosis and consequent early intervention may halt joint destruction, change the natural course of the disease by achieving prolonged remission of symptoms and obviate side effects from long-term therapy. Furthermore, 5–42% of patients with plaque psoriasis develop psoriatic arthritis and many patients are affected by psoriasis several years before developing arthritis [29]. Thus, the same concept used in rheumatology may be applied in dermatology, suggesting that early and aggressive intervention may alter the natural history of psoriasis and might prevent the development of psoriatic arthritis and consequences of the psoriasis-associated metabolic syndrome [30].

Executive summary

- Psoriasis is a lifelong, chronic and immune-mediated skin disease characterized by erythematous scaly plaques. In the USA the prevalence of psoriasis is 2.2–2.6%.
- T cells and dendritic cells (DCs) play a pivotal role in the pathogenesis of plaque psoriasis. Activated T cells in psoriatic skin produce Th-1 type cytokines, including TNF-α.
- Effector cells of innate immunity that are involved in the pathogenesis of psoriasis include neutrophils, plasmacitoid DCs and C11c+ DCs. Activated DCs produce IL-23, plasmacytoid DCs produce high levels of IFN-α, and CD11c+ DCs express high levels of TNF-α.
- Systemic treatments available for the treatment of moderate-to-severe plaque psoriasis exhibit efficacy, but are associated with specific toxicities.
- Infliximab is a chimeric anti-TNF-α monoclonal IgG_1 antibody with high affinity and avidity for soluble and cell-surface transmembrane forms of TNF-α. It is approved for the treatment of Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, psoriatic arthritis and plaque-type psoriasis.
- The first Phase II study did not show a clinically significant difference between infliximab 5 and 10 mg/kg.
- The second Phase II study showed that clinical response is higher with 5 than 3 mg/kg.
- The recommended dose is 5 mg/kg followed by additional doses at 2 and 6 weeks after the first infusion, and every 8 weeks thereafter. It is administered to patients via intravenous infusion over 2–3 h.
- The EXPRESS Phase III study showed a significant improvement of nail psoriasis at week 10, as assessed by nail psoriasis severity index.
- The most common reactions were chills, headache, flushing, nausea, dyspnea, injection-site infiltrations and high blood pressure.
- Reactivation of tubercolosis is a risk with inhibition of TNF-α. Patients with a positive protein purified derivate test may receive infliximab infusions after taking the antitubercular treatment prescribed for up to 6–9 months.

Disclosure

Alice Gottlieb holds the following: Speakers' Bureau Memberships: Amgen, Wyeth. Current Consulting/Advisory Board Agreements: Amgen, BiogenIdec, Centocor, Wyeth, Schering-Plough, Eisai, Celgene, Bristol-Myers Squib, Beiersdorf, Warner Chilcott, Abbott, Roche, Sankyo, Medarex, Kemia, Celera, TEVA, Actelion, UCB, Novo Nordisk, Almirall, Immune Control, RxClinical, Dermipsor, Medacorp, DermiPsor, Can-Fite, Incyte. Research/Educational Grants: Centocor, Amgen, Wyeth, Immune Control, Genentech, Abbott, Pharmacare.

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