

Infliximab for the treatment of plaque psoriasis

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Abstract: Infliximab is a monoclonal antibody that targets tumor necrosis factor- α (TNF α). It is used in the treatment of a number of inflammatory disorders including severe plaque psoriasis. TNF α is thought to have a major role in psoriasis by promoting an inflammatory infiltrate into the skin and inducing keratinocyte proliferation and preventing keratinocyte apoptosis, which directly contributes to the characteristic plaque skin lesions. Based on four randomized, placebo-controlled, double-blind clinical trials and nine open-label uncontrolled trials of the use of infliximab in plaque psoriasis, it was found that infliximab is a highly efficacious, rapid, sustainable, and relatively safe therapy. Yet as with any biologic, caution is recommended in its use as infusion reactions, lupus-like syndromes, infections, malignancies including lymphomas, as well as other rare events have been reported.

Keywords: infliximab, psoriasis, plaque

Psoriasis is a chronic inflammatory disease of the skin affecting at least 5.8 million people in the United States and 125 million people worldwide (National Psoriasis Foundation 2007; Gelfand et al 2005). The most common form of psoriasis, psoriasis vulgaris, occurs in more than 80% of cases. Less common forms include guttate psoriasis and erythrodermic and pustular psoriasis, which occur in approximately 10% and 3% of patients, respectively (Lebwohl 2003). Psoriatic lesions may be pruritic and disfiguring, resulting in a significant negative physical and emotional impact in those affected. Feelings of depression, fear and embarrassment, as well as dissatisfaction with disease management, are widespread among persons suffering from psoriasis (Krueger et al 2001). In 10%–30% of psoriatic patients, nail dystrophy and psoriatic arthritis cause interference with many daily activities that require both fine and gross motor skills (Nickoloff and Nestle 2004). Psoriasis cannot be explained purely by genetics (Elder et al 2001) or environment; it has a complex immunopathology that is not fully understood.

Immunopathology of psoriasis

Psoriasis results from an abnormal activation of the immune system, with T cells in the epidermis and dermis playing a central role. The initial activation of T cells is unclear, but is thought to be due to a protuberance in epidermal keratinocytes from exogenous stimuli such as trauma and UV exposure, or endogenous stimuli such as infection and medications (eg, lithium and β -blockers) which through a “danger signal” leads to the activation of antigen presenting cells (APCs) such as Langerhans cells (Matzinger 2002; Nickoloff and Nestle 2004). Once activated, Langerhans cells migrate through the lymphatic system to surrounding lymph nodes where its MHC-antigen complex is recognized by specific T cell receptors on naïve T cells. Full activation of T cells occurs with a costimulatory molecule on APCs combining with CD28 on T cells. The activated T cell expresses cutaneous lymphocyte-associated antigen (CLA) which allows access to the skin (Langley et al 2007). The abnormally activated

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T cells elaborate cytokines including tumor necrosis factor- α (TNF α) and γ -interferon which contribute to a vicious cycle of inflammation and tissue damage, manifested clinically as plaque skin lesions (Nickoloff 1991).

Role of TNF α in psoriasis

TNF α is found in high concentrations in the skin lesions and plasma of patients with psoriasis and has a major role in the stimulation and propagation of immunological activity by targeting an inflammatory infiltrate into the skin (Turbitt et al 1990). TNF α upregulates the expression of vascular endothelial growth factor (VEGF) and intercellular adhesion molecule-1/vascular cell adhesion molecule-1 which promotes angiogenesis and microvascular permeability and targeting of lymphocytes to inflammatory lesions, respectively (Markham et al 2006). TNF α induces Langerhans cell maturation and migration to lymph nodes for further T cell activation and CLA expression. TNF α further stimulates lymphocyte migration, increasing the expression of many proinflammatory cytokines including CCL27 (a skin-specific memory T cell attractant) and NF- κ B (a ubiquitous transcription factor) that leads to the expression of many gene products that mediate inflammatory responses (Banno et al 2004).

TNF α directly contributes to the characteristic plaque surmounted by silvery scales by inducing keratinocyte proliferation and preventing keratinocyte apoptosis via increasing vasoactive intestinal peptide (VIP) receptor and increasing plasminogen activator inhibitor type 2, a serine protease inhibitor, respectively (Gottlieb 2003).

The advances in the understanding of T cells and specifically TNF α in psoriasis has led to the development of biologic agents that target them (Sauder and Mamelak 2004; Chong and Wong 2007; Langley et al 2007).

Infliximab

Infliximab is a chimeric monoclonal antibody comprised of human antibody constant regions and murine variable regions that was developed to specifically target TNF α . Infliximab binds both soluble and membrane-bound TNF α , preventing it from binding its receptor which results in a decrease in epidermal T cell infiltration. There is a significant reduction of T cells in the epidermis of psoriatic lesions after 48 hours of treatment with a single, low dose (3 mg/kg) infusion of infliximab (Goedkoop et al 2004).

Infliximab helps to control angiogenesis, a key factor in the proinflammatory state of psoriasis, by down-regulating angiopoietin, a growth factor critical for new blood vessel growth, and its receptor, Tie2 (Markham et al 2006).

Furthermore, anti-TNF α drugs like infliximab have been shown to restore neuroendocrine pathways (eg, hypothalamic – pituitary – adrenal axis) from the pro-inflammatory state that TNF α favors, and normalizes hormone levels (Straub et al 2006).

Complementary to its anti-inflammatory effect that is mediated through the neutralization of TNF α , infliximab normalizes keratinocyte differentiation (Gottlieb et al 2003) and induces apoptosis of lesional keratinocytes through a caspase independent mechanism to further speed clinical improvement (ten Hove et al 2002; Kruger-Krasagakis et al 2006).

Infliximab is used to treat a number of inflammatory disorders including rheumatoid arthritis, Crohn's disease, and psoriatic arthritis (Markham and Lamb 2000; Woolacott et al 2006; Behm and Bickston 2007). In September 2006, the US FDA approved the use of infliximab in adults with chronic, severe plaque psoriasis (FDA 2006). This paper aims to review the efficacy and safety of infliximab in this setting based on a plethora of recently published research on the topic.

Randomized, placebo-controlled, double-blind clinical trials

Four randomized, controlled trials of infliximab in the treatment of plaque psoriasis have been reported in the literature (Table 1). Chaudhari and colleagues (Chaudhari et al 2001; Gottlieb et al 2003) conducted a small ($n = 33$), phase II trial consisting of a patient population with moderate to severe plaque psoriasis involving a minimum of 5% body surface area (BSA) for at least 6 months. The patients were randomly assigned to one of three groups: 5 mg/kg infliximab ($n = 11$), 10 mg/kg infliximab ($n = 11$), or placebo ($n = 11$). Infusions were given at 0, 2, and 6 weeks and followed by an open-label phase from weeks 10–26 in which relapsing patients were retreated as needed and placebo nonresponders were given an induction of infliximab. Beginning at week 2, the improvement in PASI (Psoriasis Area and Severity Index) scores were significantly ($p < 0.0003$) higher in both infliximab treated groups. At week 10, the PASI 75 (at least 75% improvement from baseline in PASI) was achieved in 82% and 73% of patients receiving 5 mg/kg and 10 mg/kg infliximab, respectively, compared to only 18% of placebo patients ($p < 0.05$). PASI 75 was maintained in 33% and 67% of the respective infliximab patients through week 26. Infusion reactions occurred in 9% of patients, but no other autoimmune events were reported. Reported adverse events (AE) were considered mild by the investigator and no serious adverse events (SAE) occurred.

Table 1 Randomized, double-blind, placebo-controlled studies of infliximab for the treatment of plaque psoriasis

Study	Population	Dose	Duration	Results (PASI 75)	Quality of life (DLQI)	Adverse effects
Chaudhari 2001; Gottlieb 2003 (phase II)	Moderate to severe plaque psoriasis involving at least 5% BSA for minimum of 6 months (n = 33)	5 mg/kg infliximab (n = 11), 10 mg/kg infliximab (n = 11), placebo (n = 11) at 0, 2, and 6 weeks; Retreatment with open label 5 or 10 mg/kg infliximab as needed for weeks 10–26	10 weeks, followed by open label extension phase through 26 weeks	Week 10: 5 mg/kg 82%, 10 mg/kg 73%, placebo 18% (p < 0.05); Maintenance of PASI 75, week 26: 5 mg/kg 33%, 10 mg/kg 67%		Generally well tolerated, no SAE
Gottlieb 2004; Feldman 2005 (phase II)	Severe plaque psoriasis for at least 6 months of at least 10% BSA and PASI of 12 or more (n = 249)	3 mg/kg infliximab (n = 99), 5 mg/kg infliximab (n = 99), placebo (n = 51) at 0, 2, and 6 weeks and an additional infusion at week 26 if static PGA (moderate/severe)	30 weeks	Week 10: 3 mg/kg 72%, 5 mg/kg 88%, placebo 6% (p < 0.001)	Week 10, percent improvement: 3 mg/kg 84%, 5 mg/kg 91%, placebo 0% (p < 0.001)	Generally well tolerated; patients that reported an AE: 3 mg/kg 78%, 5 mg/kg 79%, placebo 63% SAE: 3 mg/kg 4%, 5 mg/kg 8%, placebo 0%; Elevated LFTs: infliximab ALT 34%, AST 24%; placebo ALT 16%, AST 14%
Reich 2005 (EXPRESS I, phase III)	Moderate to severe plaque psoriasis of at least 10% BSA and 6 month duration with PASI of 12 or more (n = 378)	5 mg/kg infliximab (n = 301), placebo (n = 77) at 0, 2, and 6 weeks and every 8 weeks through week 46; at week 24, placebo patients crossed to infliximab treatment	50 weeks	Week 10: infliximab 80%, placebo 3% (p < 0.0001) Week 24: infliximab 82%, placebo 4% (p < 0.0001) Week 50: infliximab 61%		Generally well tolerated; Week 24, patients that reported an AE: infliximab 82%, placebo 71%; SAE: infliximab 6%, placebo 3%; asymptomatic increases in AST and ALT
Menter 2007 (EXPRESS II, phase III)	Moderate to severe plaque psoriasis of at least 10% BSA and PASI of 12 or more (n = 835)	3 mg/kg infliximab (n = 313), 5 mg/kg infliximab (n = 314), placebo (n = 208) at 0, 2, and 6 weeks; infliximab groups were rerandomized at week 14 to either 8 week continuous or intermittent as-needed maintenance therapy	50 weeks	Week 10: 3 mg/kg 70%, 5 mg/kg 76%, placebo 2% (p < 0.001) Week 50: 3 mg/kg: continuous 44%, intermittent 25% 5 mg/kg: continuous 55%, intermittent 38%	Week 10, infliximab groups improvement from baseline: p < 0.001 Week 50, percent improvement: 3 mg/kg: continuous 7.7%, intermittent 7.0% 5 mg/kg: continuous 7.4%, intermittent 7.7%	Generally well tolerated; Week 14, patients that reported an AE: 3 mg/kg 63%, 5 mg/kg 69%, placebo 56% SAE: 3 mg/kg 1.0%, 5 mg/kg 2.9%, placebo 2.4%; significant elevation of ALT and AST in fewer than 5% infliximab treated patients

Abbreviations: AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, physician's global assessment; LFTs, liver function tests; SAE, serious adverse events.

A larger ($n = 249$) phase II trial was conducted by Gottlieb and colleagues (Gottlieb et al 2004; Feldman et al 2005) that consisted of a study population with severe plaque psoriasis covering at least 10% BSA for 6 months or more and a PASI of at least 12. Patients were randomly assigned to either a 3 mg/kg infliximab ($n = 99$), 5 mg/kg infliximab ($n = 99$), or placebo ($n = 51$) treatment group with infusions given at 0, 2, 6 weeks, and an additional one at week 26 if a static Physician's Global Assessment (PGA) of moderate to severe psoriasis was made. At week 10, PASI 75 was achieved in 72% and 88% of 3 mg/kg and 5 mg/kg infliximab patients, respectively, compared to only 6% of placebo treated patients ($p < 0.001$). In two of the aforementioned studies (Chaudhari et al 2001; Gottlieb et al 2004), no significant differences were recorded between the two infliximab groups in inducing significant clearance, but larger dose infliximab groups, 10 mg/kg and 5 mg/kg, respectively, maintained remission longer. The Dermatology Life Quality Index (DLQI) at week 10 was improved by 84% and 91%, respectively, in infliximab treated patients compared to 0% in the placebo group ($p < 0.001$). AE and SAE were reported in 78% and 4% of the 3 mg/kg patients, 79% and 8% of the 5 mg/kg patients, and 63% and 0% of the placebo patients, respectively. The lower percentage of AE in the placebo group could be partly a result of the high dropout rate in the placebo group and thus shorter follow-up. Yet four of the SAE in the infliximab groups – squamous cell carcinoma, cholecystitis and cholelithiasis, diverticulitis, and sepsis and pyelonephritis – were considered by the investigator to be reasonably related to infliximab therapy. Infusion reactions were reported in 18% and 22% of patients in the infliximab groups, respectively, compared to 2% of the placebo group. Through week 26, 24% patients with antibodies to infliximab experienced infusion reactions compared to 22% antibody-negative patients. The only noteworthy elevated lab values were the liver function tests (LFTs) aminotransferase (ALT) and aspartate aminotransferase (AST) in the infliximab groups (34% and 24%, respectively) compared to placebo (16% and 14%, respectively).

Reich et al (2005) reported the first multicenter phase III study of infliximab [European Infliximab for Psoriasis (Remicade) Efficacy and Safety Study/EXPRESS] in patients ($n = 378$) with moderate to severe plaque psoriasis of at least 10% BSA and 6 month duration with PASI of 12 or more. Patients were randomly placed into a 5 mg/kg infliximab or placebo group with infusions given at 0, 2, and 6 weeks and then every 8 weeks through week 46. At week 24, placebo patients were crossed to receive infliximab. At week 10 and

24, PASI 75 was achieved in 80% and 82% of infliximab patients, but only 3% and 4% of placebo patients, respectively ($p < 0.0001$). At week 50, PASI 75 was achieved in 61% of infliximab-treated patients. There was generally good tolerability to infliximab with AE and SAE at week 24 reported in 82% and 6% of infliximab-treated patients and 71% and 3% placebo-treated patients, respectively. With equal follow-up, similar proportions of patients in the infliximab and placebo groups were diagnosed with infections, but serious infections were more prevalent in the infliximab group. Malignancies, squamous and basal cell carcinomas, occurred in 1% of infliximab-treated patients but 0% in placebo-treated patients. In infliximab-treated patients, 3% had infusion reactions (2% in the placebo-treated patients) and two patients had a lupus-like syndrome. No clinically significant changes in hematological values were noted except for asymptomatic increases in AST and ALT.

Menter et al (2007) performed the largest phase III trial to date ($n = 835$) with moderate to severe plaque psoriasis covering at least 10% BSA and PASI of 12 or more (Evaluation of Infliximab for Psoriasis in a Remicade Efficacy and Safety Study/EXPRESS II). Study participants were randomly assigned to a 3 mg/kg ($n = 313$), 5 mg/kg ($n = 314$), or placebo ($n = 208$) group with infusions at 0, 2, and 6 weeks. At week 14, the two infliximab groups were re-randomized to either 8 week continuous or intermittent as-needed therapy. At week 10, PASI 75 was achieved in 70% and 76% of the 3 mg/kg and 5 mg/kg infliximab-treated patients, respectively, but only 2% of placebo-treated patients ($p < 0.001$). At week 50, PASI 75 was achieved in 44% of the 3 mg/kg continuous group compared to 25% of the intermittent group, and 55% of the 5 mg/kg continuous group compared to 38% of the intermittent group. At week 10, both infliximab groups had a significant improvement in DLQI ($p < 0.001$). AE and SAE at week 14 occurred in 63% and 1.0% of the 3 mg/kg infliximab group and 69% and 2.9% of the 5 mg/kg infliximab group compared to 56% and 2.4% of the placebo group, respectively. Through week 14, 12% and 10%, in the infliximab groups, respectively, experienced an infusion reaction compared to 6% in the placebo group. While the majority of antibody-positive patients did not have an infusion reaction, an increased risk of a reaction was present in these patients compared to antibody-negative patients. Two cases of lupus-like syndrome occurred in the infliximab group compared to one in the placebo group (2:1 randomization of infliximab to placebo). Infection rates were similar in infliximab and placebo groups. Noteworthy adverse events in the infliximab group involved 2 cases of TB, 12 malignancies (1 breast carcinoma, 1 salpingeal

adenocarcinoma, 1 squamous cell skin carcinoma, and 9 basal cell skin carcinomas) compared to 0 in the placebo group, and a significant elevation of ALT and AST in fewer than 5% of infliximab-treated patients.

Open-label, uncontrolled trials

Nine open-label, uncontrolled trials of 5 mg/kg infliximab in the treatment of psoriasis have been reported (Table 2). In all trials, the majority of patients presented with plaque psoriasis but patients with erythrodermic and pustular psoriasis, acrodermatitis continua, and psoriatic arthritis are also included, and the patient population ranges from $n = 7$ to $n = 73$.

Chan and Gebauer (2003) demonstrated that a single 5 mg/kg infusion provided an average PASI and DLQI improvement at week 2 of 69% and 61%, respectively, and at week 10 ($n = 4$) of 89% and 79%, respectively, with no SAE reported.

In all the other open label studies 5 mg/kg infusions were given at a minimum of 0, 2, and 6 weeks. (Schopf et al 2002) demonstrated an average PASI improvement of 88% ($n = 8$) at week 14. PASI 75 at week 10 was achieved in 79% (Cassano et al 2004) and 77% of patients (Smith et al 2006) in trials consisting of 29 and 23 patients, respectively. At week 14, PASI 75 was achieved in 68% of patients in a trial of 28 patients (Poulalhon et al 2007). The magnitude of clinical improvement in the trials that reported PASI scores were similar to the randomized, controlled trials with PASI 75 at week 10 achieved in 76% to 88% of patients receiving 5 mg/kg infusions in these trials (Table 1).

Three trials measured improvement on the PGA scale: the first reported 88% of patients achieving almost clear improvement or better ($n = 52$) (Kalb and Gurske 2005); a second reported 75% of patients achieving excellent improvement ($n = 12$) (Ahmad and Rogers 2006); and a third reported 89% of patients achieving significant improvement after 12–14 weeks of treatment (Haitz and Kalb 2007).

Krathen et al (2006) reported that 51% of patients experienced no loss of efficacy, while 30% of patients experienced a loss of efficacy, and others discontinued their participation in the clinical trials due to adverse events or insurance difficulties.

AE were similar to those in the randomized, controlled trials with infusion reactions and infections being the most prevalent (Table 2). Serious infections included extrapulmonary tuberculosis, cellulitis (Smith et al 2006), sepsis, pneumonia, and chronic obstructive pulmonary disease (COPD) (Poulalhon et al 2007). Two studies reported elevated LFTs (Ahmad and Rogers 2006; Smith et al 2006), and one patient

with a prior history of fatty liver secondary to methotrexate and alcohol was diagnosed with autoimmune hepatitis caused by infliximab (Smith et al 2006). Reported malignancies included single cases of breast cancer (Krathen et al 2006), skin cancer, metastatic renal cell carcinoma, and CD30+ cutaneous T cell lymphoma (Smith et al 2006). The latter occurred in a 56-year-old man with a 30-year history of immunosuppressive therapies including cyclosporine, methotrexate, alefacept, and fumaric acid esters after 3 infusions of infliximab.

Efficacy

The aforementioned clinical trials (Tables 1 and 2) demonstrate that infliximab provides a rapid (as early as 2 weeks) (Chaudhari et al 2001), highly efficacious, and sustainable (up to 50 weeks) therapy especially when given at continuous (8-week) maintenance intervals (Menter et al 2007) for the treatment of moderate to severe plaque psoriasis. Infliximab use leads to a significant improvement in the quality of life as assessed by DLQI in those affected by psoriasis (Gottlieb et al 2004; Menter et al 2007). This is a very important finding considering that psoriasis has an impact on an affected persons' physical and mental functioning comparable to that seen in cases of cancer, arthritis, hypertension, heart disease, diabetes, and depression (Rapp et al 1999).

Safety

Infliximab is generally well tolerated; infusion reactions are the most commonly reported adverse events, occurring in 16% infliximab-treated patients compared to 6% of placebo-treated patients (Callen 2007). Infusion-related reactions can involve chills, fever, headache, flushing and urticaria, myalgia and arthralgia, nausea, dyspnea, and hypotension (Gottlieb et al 2004; Reich et al 2005; Menter et al 2007). Most infusion-related reactions are mild and usually can be ameliorated by reducing rate of infusion rather than discontinuing therapy. A delayed hypersensitivity reaction may also present 3–12 days after infusion and produce a serum-sickness like reaction (Krishnan and Hsu 2004).

Acute and delayed hypersensitivity reactions are partly the result of autoantibody formation towards infliximab, a concern related to the infusion of any foreign protein (Schellekens 2002). Patients with infliximab antibodies have been shown to be more likely to have an infusion reaction when compared to those with no antibodies (Menter et al 2007). However the strength of this relationship is not definitive (Gottlieb et al 2004), and even the proportion of infusion reactions in infliximab and placebo groups have shown to be similar (Reich et al 2005). This issue requires further

Table 2 Open-label, uncontrolled trials of infliximab for the treatment of plaque psoriasis

Study	Population	Dose	Duration	Results	Adverse events
Schopf 2002	Moderate to severe psoriatic skin lesions (n = 8), 2 also had PsA	5 mg/kg at 0, 2, and 6 weeks	14 weeks	PASI scores improved by 88%	No SAE
Chan 2003	Plaque psoriasis (n = 7)	5 mg/kg single dose infusion	10 weeks	Week 2, average PASI improvement: 69%; Week 10 (n = 4): 89% Week 2, DLQI improvement: 61%; Week 10 (n = 4): 79%	No SAE
Cassano 2004	14 diffuse, 13 plaque with PsA, 1 erythrodermic, 1 pustular (n = 29)	5 mg/kg at 0, 2, 6, and as-needed maintenance	10 weeks	Week 10, PASI 75: 79%	2 infections
Kalb 2005	Severe plaque psoriasis >33% BSA (n = 52)	5 mg/kg at 0, 2, 6, 14, and maintenance every 8 weeks	4–33 months, median of 22 months	88% had at least almost clear improvement on PGA scale	9 (17%) infusion reactions, 13 infections
Smith 2006	22 chronic plaque psoriasis, 1 pustular (n = 23)	5 mg/kg at 0, 2, and 6 weeks; 3 or 5 mg/kg maintenance dose every 8–10 weeks	Up to 21 months	Week 10, PASI 75: 77%	4 significant elevations in LFTs; 2 severe systemic infections: extrapulmonary tuberculosis (splenic abscess) and cellulitis, 25% discontinued therapy due to infusion reactions (2), thrombocytopenia (1), hepatitis (1), renal cell carcinoma (1), and CD30+ cutaneous T cell lymphoma (1)
Krathen 2006	Moderate to severe plaque psoriasis (n = 73)	5 mg/kg at 0, 2, and 6 weeks; maintenance dose every 5 to 8 weeks	At least 12 months	30% discontinued treatment secondary to loss of efficacy as determined by PGA; 51% no loss of efficacy	7% experienced minor AE leading to discontinuation; 4% SAE leading to discontinuation: reactivation of TB, breast cancer, GI bleeding
Ahmad 2006	10 chronic plaque psoriasis, 1 pustular, 1 acrodermatitis continua (n = 12)	5 mg/kg at 0, 2, 6, and maintenance every 8 weeks		9 had PGA of excellent improvement, 2 good PGA but became resistant, 1 failed to respond	1 infusion reaction, 1 neutropenia, 3 elevated LFTs
Poulalhon 2007	20 plaque psoriasis, 5 psoriatic erythroderma, 3 pustular psoriasis (n = 28)	5 mg/kg at 0, 2, and 6 weeks; maintenance dose every 8 weeks	22–185 weeks, median of 78 weeks	Week 14, PASI 75: 68%	18% SAE: delayed infusion reaction (1), polyarthralgias (2), infectious complications (2) 14% severe bacterial infections: community-acquired pneumonia (2), COPD (1), sepsis (1)
Haitz 2007	Chronic plaque psoriasis previously treated with etanercept (n = 19)	5 mg/kg at 0, 2, 6, and 14 weeks; maintenance dose every 14 weeks	4–25 months, median of 8 months	After 12 to 14 weeks of treatment, 89% showed a significant improvement in PGA and BSA	47% experienced minor infections

Abbreviations: AE, adverse events; BSA, body surface area; DLQI, Dermatology Life Quality Index; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; PASI, Psoriasis Area and Severity Index; PGA, physician's global assessment; PsA, psoriatic arthritis; LFTs, liver function tests; SAE, serious adverse events; TB, tuberculosis.

investigation but the potential for subsequent reactions during infusion demands close monitoring.

Another concern related to formation of antibodies to infliximab is the decreased efficacy of infliximab over time

which may require increased infusion frequencies or higher doses to maintain a clinical response and disease control (Haitz and Kalb 2007; Shear 2006). Patients with neutralizing antibodies are less likely to maintain a response to infliximab

than those negative for antibodies, but this does not determine clinical responsiveness (Reich et al 2005; Menter et al 2007). When infliximab is used in the treatment of Crohn's disease, there is a significant correlation between the development of antibodies against infliximab and increased risk of infusion reactions and shorter duration of response (Schellekens 2002). This relationship is much less clear in the treatment of plaque psoriasis as no randomized, placebo-controlled trials have been performed to date. From our experience, the frequency of infliximab administration for the treatment of plaque psoriasis should be based on clinical response rather than antibody status. We have found that when the clinical response to infliximab is waning, increasing the frequency of infliximab infusions is more effective than the addition of low dose methotrexate.

TNF α inhibition is associated with a lupus-like syndrome, which is also thought to be partly the result of an antibody response following infliximab infusion (Costa et al 2007; Ramos-Casals et al 2007). In the aforementioned randomized, controlled trials of 378 (Reich et al 2005) and 835 (Menter et al 2007) patients with psoriasis, two patients in each study had a lupus-like syndrome. It should be noted that in the latter case, one patient in the placebo group was diagnosed with the syndrome with a 2:1 randomization of infliximab to placebo (Menter et al 2007).

Infliximab's anti-TNF α effects hamper the immune system's role in defense against infections and malignancies. In the clinical use of infliximab, infection is the chief concern with upper respiratory infections being the most common (Gottlieb et al 2003; Reich et al 2005; Menter et al 2007). In the randomized, controlled clinical studies, there is no clinically significant increase in infection risk with infliximab compared to placebo (Reich et al 2005; Menter et al 2007). Yet, serious infections (Reich et al 2005) and malignancies (Gottlieb et al 2004; Reich et al 2005; Menter et al 2007) are more prevalent in the infliximab groups, demonstrating the importance of monitoring for malignancy and infection. No additional safety concerns are found for the 5 mg/kg dose compared to the 3 mg/kg dose (Menter et al 2007).

In individuals undergoing infliximab therapy for a variety of autoimmune disorders, serious infections have been seen with the following agents: *Pneumocystis jiroveci*, *Mycobacterium tuberculosis*, *Listeria monocytogenes*, *Candida albicans*, *Aspergillus fumigatus*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, and *Coccidioides immitis* – infections typical of the immunocompromised (Ellerin et al 2003; Kaur and Mahl 2007). A case of osteomyelitis in a patient without a history of

trauma who received infliximab therapy for severe psoriasis and psoriasis arthritis has recently been reported (Sri et al 2007).

Specifically, tuberculosis is a concern as TNF α plays a central role in defense against mycobacterial infections and containment of existing infections (Gardam et al 2003). The reactivation of latent tuberculosis is a well-known complication of infliximab therapy. A review of 70 cases of tuberculosis that developed after the initiation of treatment with infliximab found that the majority (56%) of patients present with extrapulmonary tuberculosis while 24% had disseminated disease, forms of tuberculosis associated with immunosuppression (Keane et al 2001). These results have been reaffirmed in subsequent clinical trials (Krathen et al 2006; Smith et al 2006). This atypical presentation as well as higher incidence of extensive infection underlines the importance of screening for tuberculosis prior to therapy by patient history, a tuberculin skin test, a chest radiograph, and maintaining a high degree of clinical suspicion throughout treatment.

MedWatch received 8 reports of lymphoma in approximately 121,000 patients (6.6/100,000) that used infliximab between May 1999 and December 2000 for rheumatoid arthritis (RA) and Crohn's disease (CD), with the lymphomas occurring within a median of 6 weeks after initiation of therapy (Brown et al 2002). It is unclear whether the lymphomas developed directly from the use of infliximab, pre-existing medical conditions, or other immunosuppressive agents that the patients were receiving. The aforementioned clinical trials of infliximab in the treatment of psoriasis documented a single case of CD30+ cutaneous T cell lymphoma in a patient previously treated with multiple immunosuppressive therapies (Smith et al 2006). Thus, the majority of data supporting a relationship between infliximab therapy and lymphoma risk comes from RA and CD patients. The risk of lymphoma in psoriasis patients treated with infliximab has not clearly been established.

Clinical trials have demonstrated a slight increase in malignancy in patients treated with infliximab. The two largest randomized, controlled clinical trials of infliximab in the treatment of psoriasis found 2% (Menter et al 2007) and 1% (Reich et al 2005) of 627 and 298 infliximab-treated patients experiencing a malignancy, respectively, compared to 0 in placebo-treated patients, the majority being skin cancers. However, long-term registry data with larger numbers of patients have not shown an association between biologic therapy and the development of solid tumors or lymphoma. There is an association with skin cancers in this registry group (Wolfe and Michaud 2007).

Much of the evidence supporting a relationship between malignancy and TNF α antagonist therapy is derived from the treatment of rheumatoid arthritis patients. A cohort study of patients treated with biologic disease-modifying antirheumatic drugs (DMARDs) including etanercept, infliximab, adalimumab, and anakinra for rheumatoid arthritis found 11 hematologic malignancies and 46 solid tumors during 2940 person-years of DMARD use, and a pooled hazard ratio of 1.37 (95% confidence interval, 0.71–2.65) and 0.91 (95% confidence interval, 0.65–1.26) for the respective malignancies when compared to methotrexate-treated patients (Setoguchi et al 2006). A review of nine randomized, placebo-controlled trials of the use of infliximab or adalimumab in the treatment of rheumatoid arthritis found a dose-dependent increased risk of malignancy in patients treated with anti-TNF antibody therapy compared to placebo with a pooled odds ratio for malignancy of 3.3 (95% confidence interval, 1.2–9.1) (Bongartz et al 2006).

Preliminary experimental evidence suggested a link between elevated TNF α and congestive heart failure (CHF) and that inhibition of TNF α could favorably modify the course of the disease (Torre-Amione et al 1996; Feldman et al 2000). This theory was discounted when three large-scale clinical trials of the TNF α inhibitors, infliximab (Chung et al 2003a) and etanercept (Anker and Coats 2002), used in the treatment of CHF were halted for lack of benefit or adverse outcomes. The infliximab trial revealed that short-term infliximab therapy did not improve patients with CHF, and high doses (10 mg/kg) adversely affected patients with CHF ($p = 0.043$) (Chung et al 2003b). MedWatch data also suggest that TNF α antagonists may induce heart failure in certain patients (Kwon et al 2003). No adverse cardiac events were reported in the trials of patients receiving infliximab therapy for psoriasis (Tables 1 and 2).

Infliximab is associated with cases of central nervous system involvement including rare demyelinating disorders (Mohan et al 2001; Robinson et al 2001). The clinical trials of infliximab in the treatment of psoriasis found that no cases of CNS disease resulted from this therapy (Tables 1 and 2). The causal relationship is weak if it exists at all, but it is recommended that the use of infliximab and other TNF α antagonists be avoided in patients with a history of demyelinating disease, and that therapy be discontinued when neurologic symptoms occur.

Elevations in serum ALT and AST are fairly commonly reported (Tables 1 and 2), but associated hepatobiliary problems are much less frequent. In a letter to healthcare professionals regarding the potential of hepatotoxicity

due to infliximab therapy, the US FDA reported 35 post-marketing and 3 clinical trial events of severe hepatitic reactions including acute liver failure, jaundice, autoimmune hepatitis, and cholestasis (Important drug warning 2004). In clinical trials of the use of infliximab in plaque psoriasis reviewed here (Tables 1 and 2), a single case of autoimmune hepatitis due to infliximab was reported in a patient previously diagnosed with fatty liver (Smith et al 2006). Hepatitis has also been reported in a patient undergoing infliximab therapy for psoriasis in the absence of autoimmune disease and previous liver damage (Wahie et al 2006). In both patients, previous methotrexate use and alcohol consumption are contributing factors. It is thought that concurrent methotrexate and infliximab therapy may exert synergistic effects on liver function, underlying the importance of close monitoring of liver function tests, especially in patients with a history of methotrexate use and alcohol consumption.

The extensive clinical trials and cases referenced above as well as physician experience has allowed the detection of the aforementioned rare adverse events. More long-term safety data has to be collected to establish a definitive relationship between these adverse events and infliximab in the treatment of psoriasis. Infliximab has generally been well tolerated in the more than 924,000 patients that have received infusions (Remicade 2007).

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