

Supplement- Psoriasis

Infliximab: Efficacy in psoriasis

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ABSTRACT

Moderate to severe psoriasis often needs to be addressed with standard disease modifying therapies such as methotrexate, cyclosporine, acitretin or ultraviolet radiation, which have their potential benefits and limitations. The tumor necrosis factor-alpha (TNF- α) is elevated in psoriatic plaques compared to non lesional skin as well as in the plasma of patients with moderate to severe psoriasis. Infliximab, a TNF- α blocker, has been recommended for the treatment of moderate to severe plaque psoriasis in adults who have failed to respond to these therapies or who cannot tolerate them. Its specific action on the bound and membrane forms of the pro-inflammatory cytokine TNF- α has made it the molecule of choice for obtaining quicker and longer remission in recalcitrant cases. However, the widespread use of infliximab in the Indian subcontinent is limited by its cost. This article reviews the international guidelines for use of infliximab, its dosage patterns, and efficacy in chronic plaque psoriasis, nail psoriasis, erythrodermic psoriasis, and pustular psoriasis as well as Indian experience.

Key words: Infliximab, psoriasis, tumor necrosis factor- α

INTRODUCTION

Psoriasis is a chronic inflammatory, immune-mediated, cutaneous disorder with multisystem comorbidities. Moderate to severe psoriasis is sometimes unresponsive or only partly controlled by standard systemic therapies like methotrexate (MTX), acitretin, cyclosporine, psoralen + ultraviolet A light (PUVA), and ultraviolet B light (UVB), which have their own limitations. Recombinant DNA (rDNA) technology enables development of biologics from cells or tissues. These molecules have target specific pharmacologic activity. rDNA technology has enabled the development of biologics that have specific pharmacologic activity offering an alternative to the way we treat severe psoriatic diseases.^[1,2] Table 1 lists the biologics available for psoriasis. The biologics

Table 1: Currently available biologics

T-cell modulating agents Alefacept, Efalizumab	
TNF- α inhibitors	Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab
IL-12 and IL-23 inhibitors	Ustekinumab
TNF: Tumor necrosis factor, IL: Interleukin	

available in India for the treatment of psoriasis are the tumor necrosis factor-alpha (TNF- α) antagonists-infliximab and etanercept. Infliximab is a chimeric human-murine monoclonal antibody (25% mouse-derived protein), whereas adalimumab is fully human. Etanercept is a genetically engineered fusion protein composed of a dimer of the extracellular portions of human TNFR2 (p75) fused to the Fc domain of human immunoglobulin G1 (IgG1).^[1,2] This article reviews the use of infliximab in chronic plaque, erythrodermic, and pustular psoriasis; its usage pattern; efficacy; and international guidelines as well as Indian experience.

NEED FOR TARGET SPECIFIC THERAPIES IN PSORIASIS

Psoriasis is considered an inflammatory autoimmune disorder that is T cell mediated.^[3] The inflammatory T helper 1 (Th1) cytokines TNF- α , as well as interleukin-12

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(IL-12) and IL-23, are necessary for its induction and maintenance of disease activity in psoriasis.^[4-7] TNF- α is elevated in psoriatic plaques compared to non lesional skin and plasma of patients with psoriasis.^[8] The serum TNF- α concentration rises with disease activity and decreases with increasing therapeutic response.^[9]

INFLIXIMAB

Chemical structure

Infliximab has a variable murine fragment antigen binding (Fab) component (25%) and a constant human component (Fc) of human IgG1 (75%), thus making it a mouse/human IgG1 isotype chimeric monoclonal antibody as shown in Figure 1. It binds specifically and with high affinity to human TNF- α and weighs 149,100 Da.^[10,11]

Mechanism of action

Infliximab can competitively block TNF- α by binding to its soluble as well as the bound transmembrane form irreversibly.^[11] It can bind both monomeric and trimeric TNF- α , in the ratio of 2:1, thus forming multimeric complexes as illustrated in Figures 2 and 3. This differentiates it from etanercept, which can block only soluble TNF- α , binding it reversibly. Once bound, the likelihood of dissociation of TNF- α from infliximab is significantly less, enabling the molecule to achieve rapid action and substantial improvement of severe psoriasis.^[12] After infliximab-TNF- α binding in the plasma and the plaques, the TNF- α cannot activate the tissue receptors. Infliximab has additional depleting effects on TNF- α producing cells causing their apoptosis by complement lysis as well as antibody-dependent cellular cytotoxicity; thus not only is the TNF- α neutralized but it cannot be biologically activated again.^[13]

Pharmacokinetics

Infliximab is available as 100 mg of preservative free powder that needs reconstitution before infusion. It is administered in the dose of 3, 5 or 10 mg/kg, diluted in 500 ml of normal saline, by intravenous infusion over 2 h, repeated at 2 and 6 weeks (the induction phase) and thereafter every 8 weeks (the maintenance phase). A mean maximum serum concentration (C_{max}) of 118 mg/ml is achieved after a single infusion of 5 mg/kg. The half-life is about 7-10 days. Post infusion, infliximab can be detected in the serum for up to 28 weeks depending on the dose and the duration of therapy.^[14] The elimination routes for infliximab have not been fully identified.^[15] Infliximab crosses the placenta and has a long half-life, but is not detected in the breast milk.^[15]

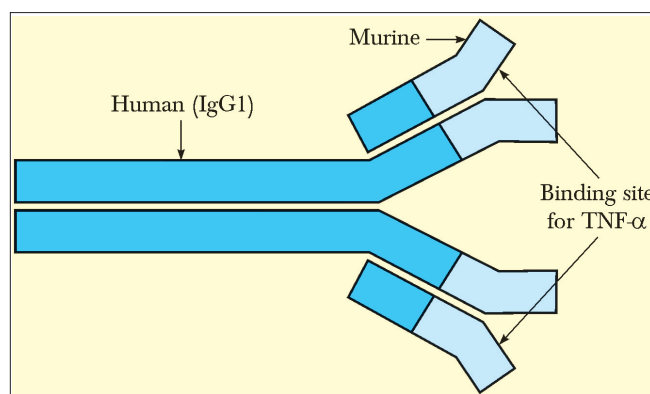


Figure 1: Infliximab structure

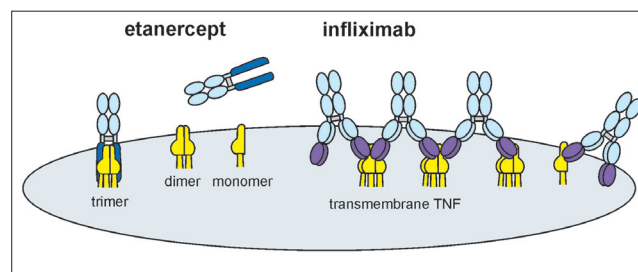


Figure 2: Infliximab binding to TNF- α receptors.

Source: *Journal of Pharmacology and Experimental Therapeutics

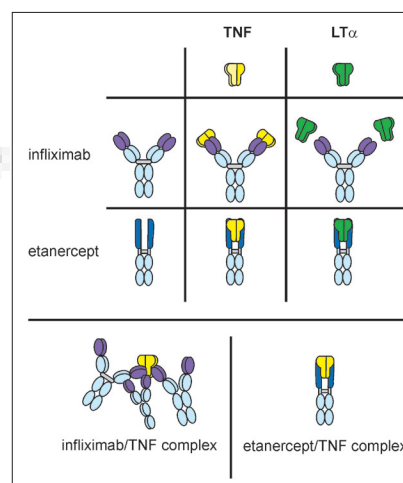


Figure 3: Difference in etanercept-TNF complex and infliximab-TNF complex.

Source: *Journal of Pharmacology and Experimental Therapeutics

Indications

In the United States and Europe, infliximab has been approved for the indications of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. In Japan, it has also been approved for intractable uveitis in Behçet's disease. The licensed indication for its use is moderate to severe plaque psoriasis and in patients who have failed to respond to, have a contraindication to or are intolerant of other systemic therapies

including cyclosporine, methotrexate, and PUVA. Some off-label uses have been reported [Table 2].^[16]

Eligibility Criteria and recommended guidelines for infliximab in psoriasis

Review of various studies from 1990 to 2011 have shown infliximab's efficacy in moderate to severe chronic plaque psoriasis with doses of 3, 5 or 10mg/kg body weight, and guidelines of criteria for patient selection and exclusion are very well defined. Biologic therapy is recommended only in recalcitrant cases of moderate to severe plaque psoriasis or variants of generalized psoriasis not responsive to conventional antipsoriatic therapies. The indications and the inclusion and exclusion criteria for the use of infliximab in psoriasis recommended by various guidelines^[9,15,17-24] are summarized in Tables 3 and 4.

Efficacy and onset of action

A favorable response is defined as either 50% or greater reduction in baseline Psoriasis Area Severity Index (PASI 50) or PASI 75, that is, improvement of 75% from baseline PASI score in chronic recalcitrant plaque psoriasis. Some trials also reported patients with a PASI 90 response.^[9,15,17-19,25] Body surface area (BSA) affected should be used when PASI scoring is not applicable as with severe disease, defined as > 10% BSA affected.^[25]

Many trials have demonstrated the efficacy of infliximab in moderate to severe chronic plaque psoriasis.^[9,17-19,26,27] Table 5 highlights the significant infliximab studies in moderate to severe psoriasis. Study by Chaudhari *et al.*^[17] was a induction study, followed by the larger SPIRIT (Study of psoriasis with infliximab induction therapy) trial.^[18] Reich *et al.*^[19] conducted the long term maintenance therapy trial whereas, EXPRESS II (European infliximab for psoriasis efficacy and safety study) trial monitored

continuous vs intermittent treatment. These extensive data studies form a basis for infliximab induction in psoriasis.^[27] According to the British and European guidelines, four randomized control trials (RCT) of very good methodological quality indicate the high efficacy of infliximab in chronic plaque psoriasis, with significant response seen within 2 weeks of infusion and the optimum response by week 10.^[15,23]

Two trials have addressed the long-term efficacy of infliximab in psoriasis. In a trial with infliximab 5, 10 mg/kg or placebo, patients who improved were evaluated for relapse (defined as loss of half the PASI improvement at week 10) at week 10-26. These patients and placebo non-responders were treated with infliximab 5 or 10 mg/kg and reassessed at week 26. Out of the 33 patients, 29 received infliximab after week 26. PASI response was maintained in 40% with the 5 mg/kg dose and in 73% with the 10 mg/kg dose.^[18] Significant long term PASI 75 response at 6 months is also highlighted in the EXPRESS trial.^[18,28] Achieving stable serum infliximab levels correlated with the maintenance of clinical response; patients who achieved a PASI 75 response by week 50 had infliximab levels of 1 mg/mL or more in their serum.^[19] Assessment of serum infliximab concentration at week 8 after treatment, the PASI 75 response rate in patients with a serum infliximab concentration of < 0.1 mg/mL, 0.1 to < 1 mg/mL, and 1 to < 10 mg/mL was 60.0% (6/10), 71.4% (5/7), and 95.7% (22/23), respectively.^[29]

The median trough concentration of infliximab was observed to be more than the limit of quantitation (0.1 mg/mL) in the infliximab group, and a steady-state concentration was maintained through week 70. The PASI 75 response rate increased with an increase in serum infliximab concentrations. At 4 weeks after the last infusion, 50% or more of the patients with a serum infliximab concentration of 0.1 mg/mL or more achieved at least a PASI 90 response.^[29]

Table 2: Clinical indications of infliximab in dermatology^[16]

FDA indications	Off label uses
Moderate to severe plaque psoriasis	Pyoderma gangrenosum
Psoriatic arthritis	Hidradenitis suppurativa
Generalized pustular psoriasis	Uveitis in Behçet's syndrome
Erythrodermic psoriasis	Vasculitis
	Graft versus host disease
	Systemic lupus erythematosus
	Sjögren's syndrome
	Sarcoidosis

Assessments of dosage pattern

Chaudhari *et al.*^[17] concluded that PASI 75 was achieved at week 10 by 73% of patients dosed at 10 mg/kg in the induction phase compared to 82% of those dosed at 5 mg/kg. Gottlieb *et al.*^[18] found the dose of 5 mg/kg to be better than 3 mg/kg for the induction phase. In a 16-week dose escalation trial to investigate withdrawal and retreatment with 10 mg/kg and 5 mg/kg of infliximab, patients who responded to treatment were withdrawn and monitored for relapse

Table 3: Summary of the inclusion and exclusion criteria for infliximab recommended in various guidelines^[9,15,17-24]

Inclusion criteria	Exclusion criteria
Age > 18 years	Absolute contraindications
Six months duration of moderate-to-severe plaque-type psoriasis unresponsive to conventional systemic treatments	History of opportunistic or chronic/recurrent severe infections, within 3 months
Negative for latent tuberculosis, after specific screening including history, physical examination and purified protein derivative (PPD) skin testing	Drug-induced psoriasis
Conventional systemic therapies to be interrupted at least 4 weeks before the first infusion of infliximab	Abnormal biochemical parameters
	Previous biologic agent therapy
	Systemic lupus erythematosus
	Heart failure (NYHA III/IV)
	Non-cutaneous malignancies
	Lymphoproliferative diseases in the previous 5 years
	Hypersensitivity to murine proteins
	Pregnancy or breast feeding
	Relative contraindications
	Demyelinating diseases
	Live vaccines
	PUVA > 200 treatments (especially if followed by cyclosporine use)
	Hepatobiliary disorders
	Hepatitis

(defined as loss of at least half of the improvement in PASI at week 10). Patients who relapsed were retreated with a single-dose infusion of their original dose. This study reported that patients in the 5 mg/kg group sustained response up to 8 weeks of drug discontinuation compared to 12 weeks for the 10 mg/kg group.^[18]

Menter *et al.*^[27] compared the efficacy and safety of continuous (every 8 weeks) and intermittent (as needed) maintenance regimens in 835 patients. One group was initiated on 3 mg/kg, another, on 5 mg/kg, and the third, on placebo. After week 14 the infliximab group was assigned either the continuous regimen or the intermittent one (as clinically needed). At 50 weeks a better response was seen with continuous dosing than with intermittent dosing in both the 3 mg/kg and 5 mg/kg groups. Thus a continuous dosing pattern seems to be more beneficial than an intermittent dosing one.

Table 4: International guidelines regarding the use of infliximab in psoriasis^[15,20-24]

Guidelines	Summary
International consensus statement by Reich <i>et al.</i> ^[21]	Patients with moderate to severe psoriasis who have failed two or more systemic therapies ^[25] Patients with a PASI of > 20 or patients with an improvement of less than 50% on this scale with previous (non) biological treatment ^[25]
British Association of Dermatologists (BAD) guideline (2009)/NICE guidelines ^[15,22]	Patients with severe disease (i.e. PASI > 10) Body surface area of 10% or greater where PASI is not applicable DLQI > 10 When standard systemic therapies are contraindicated Patients unresponsive or intolerant to standard therapy Infliximab therapy should be initiated at a dose of 5 mg/kg at weeks 0, 2, and 6 and response assessed at 3 months In patients who respond, subsequent infusions (5 mg/kg) given at 8-week intervals to maintain disease control Interrupted therapy should be avoided Methotrexate is the recommended co-medication in certain circumstances ^[26] Moderate to severe plaque psoriasis Dose of 5 mg/kg at 0, 2 and 6 weeks, and then every 8 weeks thereafter Infliximab also suitable for long-term therapy The efficacy of long-term therapy may diminish in some patients after 24 weeks of treatment
European S3 guidelines (2009) ^[23]	Clinically significant response after one to two weeks May be suitable for the treatment of severe, rare forms of psoriasis Therapy should be given continuously every 8 weeks in order to prevent infusion reactions Combination therapy with infliximab and methotrexate may help prevent the formation of antibodies Reliable contraception until 6 months after the end of treatment required in women of child-bearing potential
American Academy of Dermatology guidelines ^[24]	Moderate to severe plaque psoriasis Dose of 5 mg/kg at weeks 0, 2, and 6 and then every 6-8 weeks; dose and interval of infusions may be adjusted as needed Short-term response: 80% of patients achieved a PASI 75 at week 10; 50% PASI improvement noted by week 2 Long-term response: 61% of patients achieved a PASI 75 at week 50 Pregnancy category B

PASI: Psoriasis Area and Severity Index, DLQI: Dermatology Life Quality Index

Table 5: Summary of RCT's for infliximab in moderate to severe psoriasis.^[17,18,26,27]

Investigators, trial and year	Study group details	Dose	Efficacy	Key conclusion
Chaudhari <i>et al.</i> 2001 ^[17]	Randomized double-blind placebo controlled trial. N = 33	Infliximab; 0, 5, 10 mg/kg. Induction 0, 2, 6 week, upto 10 weeks	Patients obtained PASI 75 at week 10: 82% (5 mg/kg); 91% (10 mg/kg); 18% (placebo)	The median time to response was 4 weeks for patients in both infliximab groups
Gottlieb <i>et al.</i> 2004. SPIRIT ^[18]	Randomized double-blind placebo controlled trial. N = 249	Infliximab; 0, 3, 5 mg/kg. Induction 0, 2, 6 week. Re-infusion at 26 week (20 week treatment free interval)	Patients obtained PASI 75 at week 10: 72% (3 mg/kg); 88% (5 mg/kg); 6% (placebo)	Improvement was observed in both infliximab groups as early as 2 weeks
Reich <i>et al.</i> 2005. EXPRESS ^[26]	Randomized double-blind placebo controlled trial. N = 378	Infliximab; 0, 5 mg/kg. After induction, every 8 week (maintenance) up to 50 weeks	Patients obtained PASI 75 at week 10: 80% (infliximab); 3% (placebo); PASI 75 at week 24: 82% (infliximab); 4% (placebo); PASI 75 and PASI 90 at week 50: 61% and 45% respectively (infliximab)	Sustained PASI 75 and PASI 90 improvement through 1 year
Menter <i>et al.</i> 2007. EXPRESS II ^[27]	Randomized double-blind placebo controlled trial. N = 835	Infliximab; 0, 3 vs 5 mg/kg. After induction, every 8 week (maintenance) vs. administration. "As needed" up to 50 weeks	Patients obtained PASI 75 at week 10: 70% (3 mg/kg); 76% (5 mg/kg); 2% (placebo)	PASI responses were better maintained with continuous than with intermittent therapy within each dose, and with 5 mg/kg than with 3 mg/kg

RCT: Randomized control trial, N: total number of cases studies, SPIRIT: Study of psoriasis with infliximab induction therapy, EXPRESS = European infliximab for psoriasis efficacy and safety study, PASI = Psoriasis area and severity index

In a study by Gottlieb *et al.*^[30] infliximab was administered to all patients in three doses of 3 or 5 mg/kg as induction and then discontinued for 20 weeks. At week 10, 71.9% of patients on 3 mg/kg had PASI 75 compared to 87.9% of patients on 5 mg/kg. At week 26, 114 of 198 patients were administered a single additional infusion of infliximab; 38% of patients retreated with 3 mg/kg had clearance of lesions, compared to 64% of patients with 5 mg/kg at week 30.

In the study by Menter *et al.*^[18] relapse was reported in majority patients between week 14-22 intermittent arm (defined by loss of PASI 75) although data were not shown. A small study indicated that 50% (15/30) patients relapse (loss of PASI 75) by week 26. There are no published prospective trial data beyond 1 year.

In the maintenance phase with an evaluation after 50 weeks, the percentage of patients maintaining a PASI 75 response decreased to 61% from 80% as studied by Reich *et al.*^[19]

Guidelines from the American Academy of Dermatology (AAD), British Association of Dermatologists (BAD) and the International Consensus Panel of Dermatology experts advises dosing infliximab in a 5 mg/kg infusion schedule at 0, 2, and 6 weeks; followed by maintenance treatment every 6–8 weeks [Table 3].^[15,21,22,24] The BAD

guidelines, however, state that no studies have been performed to establish the optimal dose or frequency of repeated infusions required in order to achieve disease control.^[15,22] There are no clear recommendations on how to manage an attenuated response to infliximab.

Asian experience

There are few Asian studies of infliximab. In Japan, two clinical trials have been performed as phase III clinical trials: a randomized, double-blind, placebo-controlled multicenter clinical trial in patients with plaque psoriasis and psoriatic arthritis; and an open-label, uncontrolled multicenter trial in patients with plaque psoriasis, psoriatic arthritis, pustular psoriasis, and psoriatic erythroderma.^[29,31] In the first trial, PASI 75 response was 68.6% at week 10, compared to 0 in placebo group. The PASI 75 and PASI 90 response rates in the infliximab group were 76.7% and 56.7%, respectively, at week 66.

A study by Torii *et al.*,^[32] on 90 Japanese patients reported a rapid improvement in the PASI score and sustained response to infliximab. The PASI 75, PASI 90, and PASI 100 response rates at the complete assessment at week 66 were 66.7%, 46.7%, and 17.8%, respectively. At the end of the trial, 90% or more of skin lesions in the head region disappeared in approximately 50% of the patients, with complete disappearance in

approximately 41%. High PASI 75 and PASI 90 responses may be achieved irrespective of the body area.^[32]

In an open label pilot Indian study, Sridhar *et al.*^[33] treated three patients having moderate to severe plaque psoriasis with infliximab administered in a dose of 5 mg/kg and repeated at weeks 2 and 6. The study had two phases: A 10-week active phase, followed by a 12-week surveillance phase for relapse. During the active phase, infliximab was administered in a dose of 5 mg/kg and repeated at weeks 2 and 6. PASI was assessed at week 10. During the surveillance phase, PASI assessments were carried out at 4-week intervals until week 22 for relapse. All patients attained PASI 50 by 3.8 weeks and PASI 75 at 9.6 weeks. The mean improvement in PASI at week 10 was 77.2%. Relapse was reported at 18.6 weeks after the first infusion.

In the author's experience, most patients with moderate to severe psoriasis show a response by week 8 to 10 with an induction dose of 5 mg/kg and relapse is seen on the legs and feet about 8 weeks after the induction phase. Articular symptoms however improve within a week of the first infusion.^[34]

Efficacy and safety of infliximab vs methotrexate

In the RESTORE 1 trial, MTX-naïve patients ($N = 868$) were randomized 3:1 to receive infliximab 5 mg/kg at weeks 0, 2, 6, 14, and 22 or MTX 15 mg weekly with a dose increase to 20 mg weekly at week 6 if PASI response was $< 25\%$. At week 16, patients with $< \text{PASI } 50$ response could switch treatment groups. The primary efficacy endpoint was PASI 75 response at week 16. Major secondary efficacy endpoints were PASI 75 response at week 26. Upon conclusion of this trial, the primary end point was more likely to be achieved with infliximab than with methotrexate (78 vs 42% of patients). The incidence of adverse effects was also higher in the infliximab treated group. Infliximab was well tolerated and more efficacious than MTX in patients with moderate-to-severe plaque psoriasis. Infliximab was also efficacious in patients who failed MTX and switched to infliximab.^[35] A review by the Canadian Agency for Drugs and Technologies in Health (CADTH), based on meta-analysis of placebo-controlled trials and one RCT, noted that infliximab was more effective than methotrexate, etanercept, adalimumab and ustekinumab for the treatment of plaque psoriasis in adults.^[36] However, according to

limited data on safety, infliximab was more likely than methotrexate or 50 mg etanercept to be associated with adverse events.

Infliximab with concomitant methotrexate

Being a human chimeric monoclonal antibody, infliximab can incite neutralizing antibodies, which can be responsible for loss of efficacy with subsequent infusions in 27-47% of patients. These antidrug antibodies correlate with decreased serum infliximab levels and thus higher doses in subsequent infusions are needed.^[37] Infusion reactions are 2-3 times more likely in patients who develop antibodies. The concomitant use of methotrexate may prevent the development of these antibodies and may reduce the frequency of infusion reactions.^[38] The BAD guidelines state that concomitant systemic therapies may be indicated for some patients with very severe or unstable psoriasis. Improved efficacy with concomitant use of methotrexate is due to higher serum levels of infliximab and hence a recommendation to use smaller doses.^[15] The AAD does not recommend concomitant prescription of low-dose methotrexate, although some clinicians do so to decrease the formation of antibodies.^[24] The international consensus statement on the treatment of psoriasis with infliximab does not provide guidelines on the use of concomitant medication and infliximab.^[15,21]

Erythrodermic psoriasis

Erythrodermic psoriasis responds well and rapidly to infliximab, with clinical improvement being seen by the second infusion.^[34,39-41] According to a task force of the National Psoriasis Foundation, infliximab appears to be the most rapidly acting agent for the treatment of erythrodermic psoriasis and is recommended as a first line agent in the absence of contraindications.^[42] Takahashi *et al.*^[40] have reported that infliximab in combination with methotrexate is a promising choice for erythrodermic psoriasis. An excellent outcome at week 6, after third infusion in 7 patients with erythrodermic psoriasis was seen by treating the patients with infliximab 5 mg/kg at week 0, 2, 6 and 15 mg/week methotrexate. Heikkilä *et al.*^[41] reported similar improvement with infliximab (2.7-4.4 mg/kg) and methotrexate (5-7.5 mg/week). The combination with methotrexate reduces the risk of antichimeric antibodies. Infliximab was also successfully combined along with acitretin 0.3-0.6 mg/kg in a study by

Takahashi *et al.*^[40] on 7 patients with erythrodermic psoriasis and reported no adverse effects and good efficacy. The efficacy may be prolonged after induction when systemic therapies such as methotrexate or acitretin are combined, but long term follow-up data are scant.^[40,41] In a multicentre Japanese study, patients of erythrodermic psoriasis were assessed after infliximab at week 50 and week 66. PASI 90 responders in psoriatic erythroderma group were 37.5%.^[32]

Pustular psoriasis

The most severe variety of psoriasis is the pustular type with the generalized pustular psoriasis having severe systemic manifestations of inflammation like fever, leucocytosis, joint pains, and often intractable to standard therapies. There are several reports of the rapid and sustained efficacy of infliximab in severe pustular psoriasis,^[43-47] but most include only small numbers of patients and follow-up data is limited.^[48] Infliximab down-regulates disease-promoting chemokines such as IL-8, growth regulated oncogene-alpha (GRO- α) and monocyte chemoattractant protein-1 (MCP-1) in pustular psoriasis.^[49] It is usually administered every 6 weeks in a dose of 5 mg/kg. Routhouska *et al.*^[50] reported success with the addition of weekly, low dose methotrexate. This is echoed by the author's experience of two generalized pustular psoriasis patients who showed remarkable clinical improvement within 48 h of the first infusion and concomitant methotrexate 5 mg/week. No relapse was seen after the induction phase in two of the patients for 3 years.^[34,51]

Nail psoriasis

Nail psoriasis runs a protracted course and is difficult to treat. Although its response to infliximab was slower than that of skin plaques in a Japanese study, substantial improvement was seen with long-term therapy, even in severe cases involving all 10 finger nails.^[32] Furthermore, the improvement in NAPS (Nail Psoriasis Severity Index) score was evident in the nail matrix as well as in the nail bed, and approximately 50% of patients achieved complete clearance. In another study, over 40% of 373 infliximab treated patients with moderate to severe plaque psoriasis showed nail clearance at 50 weeks.^[52] Significant NAPS improvement at week 38 was reported in 46 patients with nail psoriasis after 6 infliximab infusions.^[53] In a small series, all 25 patients who received infusions of infliximab 5 mg/kg had clinical remission, with

a NAPS 75 by week 22, which was maintained at a follow up 12 weeks after the final infusion.^[54]

Worsening of psoriasis after infliximab

Paradoxical activation of psoriasis, including pustular psoriasis and palmoplantar pustulosis, with infliximab treatment has been occasionally observed in adults and in children.^[55-60] Mössner *et al.*^[57] reported 5 patients with chronic plaque-type psoriasis who developed palmoplantar pustulosis during or after discontinuation of infliximab therapy. In two of the five cases, manifestation of palmoplantar pustulosis was not accompanied by worsening of plaque-type psoriasis. This study postulates that site-specific factors or a differential contribution of immunological processes modulated by TNF- α inhibitors to palmoplantar pustulosis and plaque-type psoriasis may be responsible for this expression.

Wollina *et al.*^[58] reviewed TNF- α antagonist induced psoriasis or psoriasiform eruptions in 120 patients, including 63 on infliximab. In 74 patients, the psoriasis was newly diagnosed and in 25, there was exacerbation or aggravation of pre-existing psoriasis. Withdrawal of the implicated TNF- α inhibitor in 47 patients alone or in association with adjuvant anti-psoriatic topical therapy resulted in complete remission in 21 patients, partial remission in 20, and stable disease in another three. Patients who develop psoriasis or a psoriasiform eruption during treatment with one TNF- α blocker may respond to an alternative TNF- α antagonist without any adverse event.^[59,60] In children, infliximab induced psoriasis may be present with involvement of the scalp^[61] or face.^[55]

Pediatric psoriasis

Infliximab has been used for Crohn's disease in children older than 6 years. Though there are no trials of its use for psoriasis in children, there are several reports of its successful use in psoriasis. Three cases have been reported, all the treated children were above 8 years of age. Two of chronic plaque recalcitrant psoriasis and another of generalized pustular psoriasis. Two patients were treated with induction dose 3mg/kg and one with 5 mg/kg and maintenance at intervals 8 weeks. Improvement was reported in all the cases. Recurrence was seen on scalp and limbs after 10 months in the patient with pustular psoriasis and was controlled with addition of methotrexate.^[61-64]

Pregnancy and lactation

According to European guidelines, infliximab is not recommended during pregnancy or breastfeeding (FDA pregnancy category B). Because of the long half-life of the product, reliable contraception is required in women of childbearing potential until 6 months after the last infusion.^[23]

In BAD guidelines infliximab is not recommended in pregnancy and lactation. There are no prospective or retrospective trials that have been conducted for the treatment of psoriasis during pregnancy with infliximab. Several publications concerning the outcome of pregnancy following exposure to TNF antagonists are reported in Crohn's disease and arthritis. Although these patients, in contrast to patients with psoriasis, are more likely to have been exposed to combination therapy.^[15]

Lactation safety is unknown according to various guidelines.^[15,21,22,24]

CONCLUSION

Infliximab is the biologic therapeutic option for patients with moderate to severe psoriasis that is non-responsive to conventional antipsoriatic agents. Infliximab is extremely effective and has a rapid onset of action. The response is usually evident by the second week of treatment. There are little data related to the use of infliximab for moderate to severe psoriasis in Indian patients, but anecdotal reports indicate its efficacy and rapid onset of action. International guidelines recommend standard dose used is 5 mg/kg body weight. Standard induction is of 3 doses. Choice between intermittent or continuous dosing pattern is dependent on clinical response and maintenance of response, taking into consideration the safety issues and prevention of potential antichimeric antibody development. Infliximab is an excellent option for generalized pustular and erythrodermic psoriasis that are recalcitrant to standard anti-psoriatic therapy. A vial of 100mg costs 34,000 INR. For an average Indian weighing 70 kg, one induction dose of 5 mg/kg is approximately 136,000 INR. In India prospective studies are needed to establish the efficacy and safety of biologics in recalcitrant moderate to severe plaque psoriasis.

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