
Infliximab in the treatment of moderate to severe atopic dermatitis

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Background: Chronic use of standard therapies for atopic dermatitis (AD) is associated with variable efficacy and potential side effects. Targeted therapeutic approaches, such as the inhibition of tumor necrosis factor- α , may be a novel option.

Objective: This investigator-initiated, open, prospective, single-center, pilot study was conducted to evaluate the long-term efficacy and safety of infliximab in patients with AD.

Methods: Nine patients with moderate or severe AD were enrolled. AD in these patients was resistant to conventional therapy. Infliximab 5 mg/kg was administered by intravenous infusion at weeks 0, 2, 6, 14, 22, 30, and 38, and patients were followed for 46 weeks.

Results: Induction therapy with infliximab significantly improved all clinical parameters, but this improvement was not sustained through maintenance therapy. Only two patients with severe AD achieved an excellent clinical response by 46 weeks.

Conclusions: Infliximab monotherapy may be an additional therapeutic option for the management of refractory severe AD. (J Am Acad Dermatol 2005;52:522-6.)

Atopic dermatitis (AD) is a highly pruritic chronic inflammatory skin disease that affects 10% to 20% of children and 1% to 3% of adults. AD is characterized by erythematous papular or vesicular lesions in the acute form of the disease and by lichenified areas in the chronic form. The course of the disease may be constant over prolonged periods of time or it may be of a relapsing and remitting nature. Standard therapy for AD is associated with variable efficacy. Potential side effects of prolonged treatment with glucocorticoids are skin atrophy and suppression of the hypothalamic-

pituitary-adrenal axis. Immunosuppressive drugs such as cyclosporin and methotrexate have been associated with organ toxicity and the risk for infections. In light of the chronic and relapsing nature of AD, there is an interest in identifying novel effective and well-tolerated therapeutic options.¹⁻³

In the pathogenesis of AD, tumor necrosis factor- α (TNF- α) is released initially by infiltrating mast cells and later by invading T-helper lymphocytes as well as epidermal keratinocytes. TNF- α is involved in the up-regulation of proinflammatory cytokines, such as interleukins (ILs)-1, -6, -8, and of adhesion molecules, such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM), on keratinocytes and vascular endothelial cells, thereby facilitating the migration and adhesion of inflammatory cells in the epidermis. Patients with AD reportedly have significantly elevated serum and tissue concentrations of TNF- α and, thus, may be responsive to treatment with TNF- α -inhibitors.^{1,4,5}

Infliximab is a chimeric monoclonal antibody that consists of a murine F_{ab}-portion specific for human TNF- α and the constant region (F_c) of human IgG₁. Infliximab binds with high specificity and affinity to free and membrane-bound TNF- α . Infliximab has

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Table 1. Clinical response to infliximab treatment in 9 patients with atopic dermatitis through week 46

	Patient								
	1	2	3	4	5	6	7	8	9
Age y/sex	23/M	57/F	35/M	22/F	24/F	19/M	35/M	59/M	60/M
IGA	4	4	3	3	3	4	4	4	3
EASI									
Week 0	20.4	23.5	10.7	19.3	20.5	30.3	34.8	24.6	18.8
Week 2	17.1	7.2	12.4	25.2	8.4	4.1	2.5	8.2	10.7
Week 10	13.4	4.5	16.6	16.8	24	7.0	26.1	7.5	20.1
Week 22	19.5	18.7				1.0		19.0	
Week 46		6.5				2.3			
PSA									
Week 0	3	2	3	3	3	3	3	3	2
Week 2	3	0	3	1	2	0	0	2	2
Week 10	2	0	1	2	3	0	2	2	3
Week 22	1	3				0		2	
Week 46		1				0			
DLQI									
Week 0	27	14	15	26	21	11	25	16	16
Week 2	27	5	17	14	8	9	18	16	17
Week 10	9	3	16	5	19	3	19	8	16
Week 22	9	20				2		12	
Week 46		1				4			
Eosinophils (%)									
Week 0	3	0	0	0	6	15	25	10	5
Week 2	0	0	7	0	3	8	10	11	2
Week 10	0	1	0	0	1	15	10	9	0
Week 22	0	0				3		5	
Week 46		0				5			
CRP (mg/L)									
Week 0	20	<2	<2	3	4	4	<2	4	<2
Week 2	25	<2	6	<2	<2	<2	<2	<2	<2
Week 10	4	<2	4	<2	<2	<2	<2	6	<2
Week 22	6	<2				<2		3	
Week 46		<2				<2			
ECP (μg/L)									
Week 0	110	73	24	72	41	126	39	100	84
Week 2	93	38	116	86	8	39	42	200	71
Week 10	87	71	109	54	65	91	22	113	92
Week 22	42	51				14		46	
Week 46		51				54			

CRP, C-reactive protein; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECP, eosinophilic cationic protein; IGA, Investigator's Global Assessment; PSA, Pruritus Severity Assessment.

a dual mode of action: (1) blocking soluble TNF- α ; and (2) inducing lysis of TNF receptor bearing target cells, which requires activation of complement.⁶ Blockade of TNF- α inhibits the migration of leukocytes and the release of additional TNF- α -dependent proinflammatory cytokines, such as IL-1, IL-6, and IL-8. Currently, infliximab has been approved for the treatment of severe Crohn's disease and active rheumatoid arthritis (RA) in adults (≥ 18 years of age).^{7,8} Recently, controlled studies have

demonstrated the efficacy of infliximab in psoriatic arthritis and psoriasis vulgaris.^{9,10,11} In addition, infliximab has proven efficacious in several TNF- α -associated inflammatory skin disorders.¹²⁻¹⁵

METHODS

This was an investigator-initiated, open, prospective trial conducted at a single center, the Department of Dermatology, University of Erlangen-Nürnberg, Germany. Nine patients (6 men and 3 women, aged

19–61 years) with moderate ($n = 4$) and severe ($n = 5$) AD according to the Investigator's Global Assessment (IGA) score (moderate: IGA = 3; severe: IGA = 4) were enrolled. These patients had AD that was resistant to conventional therapy (topical glucocorticoids, ultraviolet-therapy). An Institutional Review Board approved the study design, and all patients gave informed consent before entering the study. Infliximab 5 mg/kg was administered via 3 intravenous infusions at weeks 0, 2, and 6 for induction therapy. Patients were assessed at week 10 for the primary study endpoint. Additional infusions of the same dose were given via 4 infusions at weeks 14, 22, 30, and 38 for maintenance therapy. Patients were assessed at week 46 for the secondary study endpoint. The following exclusion criteria were ruled out before treatment with infliximab: pregnancy, ultraviolet treatment, topical high-potency steroid treatment, systemic administration of antibiotics, severe asthma, infectious disease (tuberculosis), congestive heart failure, and history of demyelinating disease and malignancies. During the study, only inert emollients and low potency topical glucocorticoids (1% hydrocortisone acetate in unguentum leniens) were allowed as additional treatment.

Improvement or worsening of AD was monitored based on the following assessments: Eczema Area and Severity Index (EASI), Pruritus Severity Assessment (PSA), and Dermatology Life Quality Index (DLQI). Response was defined as a reduction of EASI score by $\geq 50\%$ (excellent), by 30 to 49% (moderate), or by $\leq 29\%$ (nonsignificant). AD patients who were classified as “responders” (reduction of EASI $\geq 30\%$) at week 10 entered a retreatment phase lasting up to week 46.

Immunoserologic parameters were monitored to evaluate the inflammatory reaction (Table I). Parameters included blood eosinophil count (%), serum C reactive protein (CRP; mg/L), and eosinophilic cationic protein level (ECP; $\mu\text{g/L}$). Safety was assessed by summarizing incidence and nature of adverse events. Patients were assessed via individual scores up to week 46. Furthermore statistical analyses were performed using the Wilcoxon signed rank test ($P < .05$) to compare assessments at designated study time points (weeks 2, 6, and 10) compared to baseline (week 0).

RESULTS

At week 2, infliximab showed a significant clinical efficacy as assessed by EASI ($P = .03$) in all 9 AD patients; mean EASI scores decreased from 22.5 (week 0) to 10.6 (week 2) following infliximab therapy, indicating improvement of at least 53%. The

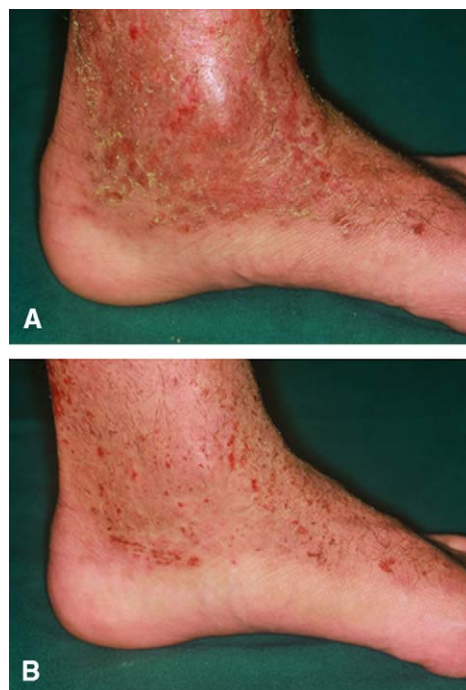


Fig 1. Temporary clinical improvement of severe AD in a 23-year-old male. Eczematous skin lesions that had been present for 9 months on both feet at baseline (**A**) were markedly reduced at week 10 (**B**) after 3 infusions with infliximab (5 mg/kg). This effect was not sustained during maintenance therapy.

group of 5 patients with severe AD showed a significant decrease in mean EASI scores from week 0 to week 2 (26.7 to 7.8; $P = .02$), while the 4 patients with moderate AD were less responsive (17.3 to 14.2). At weeks 10, 14, and 30, 6 patients were withdrawn ($n = 4$, moderate AD; $n = 2$, severe AD) based on an EASI reduction of $\leq 29\%$ and one patient was excluded at week 10 because of a serious infusion reaction. Two patients with severe AD (patients 2 and 6) completed the study at week 46 with an excellent response and EASI scores of 6.5 and 2.3 (Table I).

Pruritus, as assessed by PSA, significantly improved in all patients with AD at week 2 (1.4; $P = .03$) and week 10 (1.6; $P = .04$) compared with week 0 (2.8). Pruritus was significantly reduced at week 2 by 64.3% (PSA: 2.8 to 1.0) in patients with severe AD compared with 28.6% in patients with moderate AD. At secondary study endpoint, PSA scores were extremely reduced in the two remaining patients with severe AD (Table I).

The beneficial effect of infliximab therapy on the subjective well being of patients was demonstrated by the significant reduction from baseline in DLQI scores among all patients at week 10 (week 0: 19; week 10: 10.9; $P = .02$). This reduction in DLQI was



Fig 2. Long-term clinical improvement of severe AD in a 19-year-old male. The patient had severe AD of the neck (**A**) for 3 years that was unresponsive to conventional therapy. Following infliximab therapy (5 mg/kg), there was a significant clearing of all lesions at week 10 (**B**). This effect was sustained over 46 weeks.

based primarily on a decrease in pruritus. Patients with severe AD showed a more pronounced DLQI reduction than did patients with moderate AD (week 10: 8.4 versus 14.9). At week 46, the DLQI scores in the two remaining patients with severe AD decreased considerably (Table I).

Thus, infliximab showed an overall significant but clinically moderate effect in patients with moderate to severe AD based on EASI and PSA at week 2 and on PSA and DLQI at week 10 (EASI: $P = .03$, PSA: $P = .03$, DLQI: $P = .08$ [week 2 versus week 0]; EASI: $P = .07$, PSA: $P = .08$, DLQI: $P = .06$ [week 6 versus week 0]; EASI: $P = .09$, PSA: $P = .04$, DLQI: $P = .02$ [week 10 versus week 0]; Figs 1 and 2).

Blood eosinophil counts, serum CRP, and ECP levels showed no significant decrease from baseline at any time point over the 46 week study period. Upon termination of infliximab therapy, eosinophil counts and ECP levels showed a small increase (Table I). Serum and urine assessments, including hemoglobin, leukocyte counts, and hematocrit, were normal at all visits (not shown).

The safety profile of chronic infliximab treatment was evaluated based on the incidence of adverse events. During this 46-week study, 3 patients reported either headache ($n = 2$) or nausea ($n = 1$),

which did not require medical intervention and were classified as mild adverse events. Following the week 6 infliximab infusion, one patient experienced temporary flush and dyspnea, which resolved spontaneously upon discontinuation of the infusion. This patient was withdrawn from the study at week 10.

DISCUSSION

T-helper type 2 cell (TH2) and TH1 cytokines contribute to the pathogenesis of skin inflammation in AD, which depends on the duration of the skin lesion. Patients with acute AD have a systemic TH2 response with elevated serum IgE levels, eosinophilia, and marked infiltration of TH2 cells into acute skin lesions with a predominance of IL-4, IL-5, IL-10, and IL-13 expression. Especially children show this pattern of AD with high serum IgE levels strongly associated with the prevalence of asthma.^{1,2} However, with the infiltration of eosinophils and macrophages in chronic AD, there is a rise in IL-12 expression and a switch to TH1 cellular responses. Chronic AD skin lesions as often seen in adults with a prolonged duration of disease have increased numbers of IL-1, IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-12, interferon (INF)- γ and TNF- α expression. This biphasic

TH2/TH1 switch in immune response is characterized by lichenification, epidermal hyperplasia, and dermal fibrosis.^{1,2} TNF- α is a key regulator of inflammation and also plays a major role in the development of chronic AD. On one hand, this could explain the benefit of the two patients with severe chronic AD to infliximab therapy. On the other hand, disrupting the TH2/TH1 balance by downregulating TH1 cytokines may result in manifestations of TH2 disease. This hypothesis could be an explanation for the lack of efficacy to infliximab therapy in most patients with especially moderate AD during maintenance therapy. Furthermore cases of atopic dermatitis-like eruptions precipitated by infliximab infusions have been reported lately.^{16,17} Regarding the safety profile, chronic infliximab treatment has been associated with side effects, such as infection, including reactivation of tuberculosis; infusion reactions; and various cutaneous manifestations.^{15,18} Current recommendations and contraindications of anti-TNF- α treatment from the International Consensus Group can be retrieved from the internet at www.rheumanet.org.

The results of this study show that an induction regimen with infliximab monotherapy at weeks 0, 2, and 6 improved all AD parameters measured in this study. At week 2 not only clinical scores were markedly reduced, but also eosinophils and serum CRP levels showed a decrease. Therefore, infliximab monotherapy may prove to be an additional therapeutic option for the management of refractory severe AD. Efficacy was not sustained during maintenance therapy. Of note, two patients with severe AD seemed to show greater benefit to this therapy up to week 46. However, additional study data from a larger patient cohort are required to confirm these observations. This analysis should include an evaluation of clinical efficacy and safety, as well as the reduction in cost associated with the in- and out-patient care of individuals with severe AD. Furthermore we have to consider whether the patients with AD developed anti-TNF- α antibodies. This could explain the lack of efficacy in infliximab maintenance therapy in most patients. Infliximab has been routinely prescribed with methotrexate for RA. There is some evidence that methotrexate used with infliximab prevents the development of anti-chimeric antibodies.^{7,19} Clinical trials examining the concomitant prescription of these two agents in AD could become an option. Another possible alternative for preventing relapses of this skin disorder is the reduction of the dosing interval in infliximab maintenance therapy from every 8 weeks to every 4 or 2 weeks. Future studies should focus at these issues to clarify the value of treatment with infliximab in AD.

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