

Predictive Factors of Eczema-Like Eruptions among Patients without Cutaneous Psoriasis Receiving Infliximab: A Cohort Study of 92 Patients

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Key Words

Anti-tumor-necrosis-factor therapy • Infliximab • Eczema • Atopy • Adverse drug reaction

Abstract

Background: Anti-tumor-necrosis-factor- α agents are limited by their side effects. Eczema is one of the most frequent adverse reactions affecting quality of life. **Objective:** To assess potential predictive risk factors for eczema in patients receiving infliximab. **Methods:** We conducted a prospective cohort study including patients treated with infliximab for a variety of disorders with the exception of cutaneous psoriasis. Clinical features were compared among patients with and without eczema under therapy. **Results:** 92 consecutive patients were included; 15 developed eczema after the initiation of infliximab. In univariate analyses, a personal history of atopic symptoms was the only predictive factor for the occurrence of eczema (odds ratio = 3.6). Sex, age, principal diagnosis, dose and duration of infliximab and concomitant use of other immunosuppressors had no influence on the occurrence of eczema. **Conclusions:** A personal history of atopic symptoms is predictive of eczema under infliximab. Specific information should be provided to atopic patients starting such a treatment.

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Introduction

Tumor necrosis factor α (TNF) plays a critical role in the pathogenesis of various inflammatory or immune-mediated diseases such as rheumatic or intestinal diseases. Therefore, anti-TNF agents have a dramatic effect on the activity of these diseases since they inhibit the functional activity of this cytokine. Infliximab is an anti-TNF monoclonal antibody binding to the soluble and transmembrane forms of TNF and inhibiting the binding of the cytokine to its receptor. It is currently approved for the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriasis and ulcerative colitis [1]. The safety profile of this drug seems to be favorable. However, severe side effects have been reported, including common and opportunistic infections, malignancies, demyelinating disease, lupus-like syndromes and congestive heart failure [2, 3]. Cutaneous adverse drug reactions, although less severe, are much more frequent and may dramatically affect the patients' quality of life. Infectious skin disorders have been largely reported [4]. Other

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skin side effects are psoriasis or leukocytoclastic vasculitis [4, 5]. In a few studies, the most frequently described adverse event in patients receiving anti-TNF therapy is eczema-like eruption, which affects 15–23% of treated patients [6, 7]. Some of these eczema-like reactions have been reported as atopic dermatitis eruptions with flexural involvement [8]. However, their predictive factors have not yet been explored. In the present study, we prospectively evaluated a cohort of patients for skin manifestations to assess potential predictive clinical factors.

Methods

Patients

In a prospective cohort study from September 2007 to February 2008, all consecutive patients attending the Departments of Rheumatology and Gastroenterology of Saint-Antoine Hospital (Paris, France) for infliximab infusion for at least 2 months were included. Data were collected prospectively, using a standard anonymous form for each patient according to the current regulations regarding patient consent and information. The following criteria were recorded for each patient: age, sex, principal disease receiving treatment, duration of infliximab therapy in months, average dose of infliximab administration in mg/kg/8 weeks, presence of eczema-like lesions, initiation of eczema before or after anti-TNF therapy, use of concomitant drugs such as methotrexate, azathioprine or corticosteroids. Eczema-like lesions were defined as pruriginous ill-limited plaques with erythematous or squamous papules, macules or vesicles. In addition, we collected for each patient the history of personal and family atopy as defined previously [9, 10]. In particular, patients were asked whether they had had a diagnosis or symptoms of allergic asthma, allergic rhinitis or atopic dermatitis.

Statistical Analyses

The baseline characteristics of patients were compared between groups with and without eczema-like lesions. According to statistical conditions, the χ^2 or the Fisher tests were used for qualitative variables. The Student or the Mann-Whitney tests were used for quantitative variables. Studied variables included principal disease, age, dose and duration of infliximab therapy, personal or familial history of atopy, and concomitant use of methotrexate, corticosteroid and azathioprine. All tests were two-sided with $p < 0.05$ considered statistically significant. Odds ratios and 95% confidence intervals (CIs) were estimated.

Results

Baseline Characteristics

A total of 92 patients (54 women and 38 men) were included during the 6-month study period (table 1). Patients were affected mainly by Crohn's disease (51 cases, 55%) and rheumatoid arthritis (21 cases, 23%). None was

Table 1. Baseline characteristics of 92 patients undergoing infliximab therapy

Variables	Number	Percentage
Females/males	54/38	59/31
Mean age $\pm$ SD, years	43.1 $\pm$ 16.2 (range: 18–83)	
Mean duration of infliximab treatment $\pm$ SD, months	32.1 $\pm$ 26 (range: 2–98)	
Mean dose of infliximab treatment $\pm$ SD, mg/kg/8 weeks	5.6 $\pm$ 1.8 (range: 2.4–12)	
Principal diagnosis		
Crohn's disease	51	55
Rheumatoid arthritis	21	23
Ankylosing spondylitis	9	10
Ulcerative colitis	8	9
Psoriatic arthritis	3	3
Eczema-like eruption	19	21
After anti-TNF	15	16
Personal history of		
atopic symptoms	16	17
Family history of atopy	11	12
History of contact dermatitis	4	4
Additional therapy		
Methotrexate	21	23
Corticosteroids	15	16
Azathioprine	4	4

SD = Standard deviation.

affected by cutaneous psoriasis. The median age of patients was 41 years (range 18–83), the median duration of infliximab treatment was 26 months, and the mean dose of infliximab ($\pm$ SD) was 5.6 $\pm$ 1.8 mg/kg/8 weeks. In addition to infliximab, 21 patients (23%) received methotrexate, 15 patients (16%) systemic steroids and 4 patients (4%) azathioprine.

Main Outcome

Eczema was recorded overall in 19 patients (20.6%). Lesions were reminiscent of atopic dermatitis since they could be found in popliteal, antecubital or retroauricular flexures (fig. 1). Histology obtained from 2 patients displayed typical spongiosis and exocytosis with persistent granulosis and an absence of parakeratosis, clearly showing features of eczema and ruling out psoriasis as an alternate diagnosis (fig. 1). As a comparison, paradoxical pustular psoriatic eruptions of palms and soles occurred only in 1 patient. Among patients presenting eczema-like reactions, 15 (79%) presented their initial manifestations after the introduction of infliximab therapy. 16 patients had a history of atopic symptoms such as childhood atop-

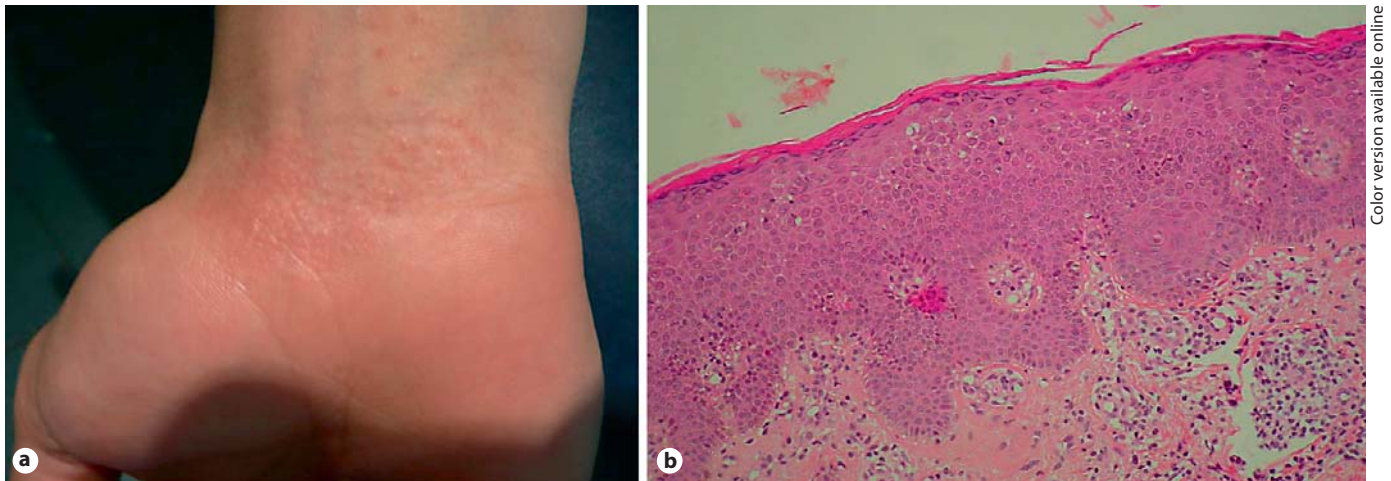


Fig. 1. **a** Flexural erythematous and vesicular plaques appearing within months after the start of anti-TNF therapy. **b** Histological features of eczema under anti-TNF therapy display spongiosis with dermatitis and exocytosis. The persistence of the granular layer and the absence of parakeratosis rule out psoriasis as an alternate diagnosis.

ic dermatitis (n = 8), asthma (n = 7) and allergic rhinitis (n = 7); 11 had a family history of atopy. Finally, 4 patients had a history of contact dermatitis.

Predictive Factors

We next examined variables potentially predictive of the occurrence of eczema under infliximab therapy (table 2). We therefore excluded the 4 patients who had had eczema before the initiation of infliximab. The occurrence of eczema-like lesions was not influenced by the patient's age, dose or duration of infliximab treatment or concomitant immunosuppressive therapies.

Personal history of atopic symptoms was the only variable significantly associated with eczema-like lesions after infliximab therapy ($p = 0.04$; odds ratio = 3.6, 95% CI = 1.0–12.8). Of note, most patients with a history of atopic symptoms had allergic rhinitis. Two out of 15 patients with eczema had a history of atopic dermatitis in their childhood without any flare in recent years. A family history of atopy was not associated with eczema. The positive predictive value of a personal history of atopic symptoms on the occurrence of eczema was 35.7% (95% CI = 17.5–56.6) and the negative predictive value was 86.5% (95% CI = 83.0–90.4). The initial diagnosis of rheumatoid arthritis tended to be associated with the occurrence of eczema-like lesions, although this trend did not reach statistical significance. Of note, 20% of patients with rheumatoid arthritis were atopic.

No patient stopped infliximab therapy because of the dermatological events. Most eczematous lesions were treated by topical steroids with a good response.

Discussion

The broad use of anti-TNF agents results in the occurrence of many side effects. Eczema-like eruptions are among the most frequent adverse events reported during anti-TNF therapy [4]. In the present study, we prospectively examined a cohort of patients receiving infliximab and showed that a history of atopic symptoms is predictive of the eczema-like eruption under infliximab therapy. Our study was performed on patients with different primary diseases with the exception of cutaneous psoriasis. We decided to focus on infliximab only to have interindividual consistency. As reported previously, eczema-like eruptions occur with other anti-TNF agents as well [4, 11]. However, their association with atopy in the context of these different drugs remains to be demonstrated.

Our study was designed to prospectively collect information from patients on a real-life interrogation basis. This means that the definition of atopic symptoms corresponded to information that could be obtained by questioning the patient and there were no biological tests involved. The questionnaire used here was based on validated questions in the International Study of Asthma and Allergies in Childhood [10]. In addition, it has also been

Table 2. Factors associated with eczema-like eruptions occurring under infliximab therapy

Variables	Absence of eczema-like eruptions (n = 73)	Presence of eczema-like eruptions (n = 15)	p (bilateral)
Females (n = 51)	43 (59)	8 (53)	0.69
Age, years	43	42	0.70
Duration of infliximab treatment, months	31	38.7	0.29
Dose of infliximab treatment, mg/kg/8 weeks	6.0	5.0	0.22
Principal diagnosis			
Crohn's disease (n = 48)	42 (57)	6 (40)	0.21
Rheumatoid arthritis (n = 20)	14 (19)	6 (40)	0.08
			OR = 2.8, 95% CI = 0.9–8.9
Ankylosing spondylitis (n = 9)	7 (10)	2 (13)	0.65
Ulcerative colitis (n = 7)	6 (8)	1 (7)	0.80
Personal history of atopic symptoms (n = 14)	9 (12)	5 (33)	0.04
			OR = 3.6, 95% CI = 1.0–12.8
Family history of atopy (n = 10)	7 (10)	3 (20)	0.36
Additional therapy			
Methotrexate (n = 20)	17 (23)	3 (20)	1.0
Corticosteroids (n = 14)	11 (15)	3 (20)	0.7
Azathioprine (n = 2)	2 (3)	0 (0)	1.0

OR = Odds ratio. Figures in parentheses indicate percentages of all patients.

shown recently that predictive values of skin atopy patch tests and allergen-specific IgE are estimated to be 45 and 64%, respectively, making it difficult to use them for diagnostic purposes [12]. Despite these limitations, this study more closely reproduces the actual and appropriate clinical setting for the care of patients under anti-TNF therapy.

Eczema-like eruptions were histologically analyzed only in a few patients, and psoriasis was ruled out as a differential diagnosis. This might be due to the absence of psoriatic patients in our cohort. Previous reports of eczema under anti-TNF therapy have also reported histology of these lesions. They all showed typical features such as dermatitis and spongiosis, with high dermal perivascular infiltration [7]. The occurrence of psoriasis under anti-TNF therapy has been well investigated. Its incidence is low and has recently been estimated to be 1.04/1,000 patient-years [13]. Its clinical and histological features are highly reminiscent of similar types of psoriasis in the absence of treatment [14]. Overall, the above-mentioned data rule out psoriasis as an alternate diagnosis in our cohort patients. In addition, cutaneous moderate to severe psoriasis is also a target of infliximab

therapy [15]. Our study did not address whether eczema-like eruption may as well occur in patients affected by cutaneous psoriasis and treated with infliximab for obvious confounding issues. If this is to occur, current guidelines clearly favor the continuation of therapy if this is beneficial to the patient [15].

Previous studies reporting the occurrence of eczema-like eruptions under anti-TNF therapy have also suggested that the topography of these lesions was reminiscent of atopic dermatitis [10]. Lee et al. [4] reported that eczematous lesions were primarily located in the antecubital and popliteal fossae. Similarly, under etanercept or infliximab treatment, atopic-dermatitis-like lesions have been reported [8, 11, 16, 17]. These previous reports and our current findings may suggest a possible flare of a pre-existing atopy under infliximab. However, this remains to be demonstrated, in particular regarding other atopic symptoms such as asthma or rhinitis.

In a recent study, there was no statistical difference in the prevalence of atopic dermatitis, xerosis and eczema in patients with rheumatic diseases treated or not with anti-TNF agents [18]. Interestingly, rheumatoid arthritis is a disease associated with a low prevalence of atopic derma-

titis, as reported by Hilliquin et al. [19]. Of note, there is a trend in our study suggesting that under infliximab therapy, patients with rheumatoid arthritis therapy are more at risk of developing eczema. This is probably due to an overrepresentation of atopy within our cohort (20%) affected by rheumatoid arthritis compared to previous studies by Hilliquin et al. [19] (7%) or Rudwaleit et al. [20] (13%). Other situations have been reported to trigger eczema-like lesions. Therapy with α -interferon – another immunomodulatory agent – has often been associated with the occurrence of dermatitis (about 20%) [21]. Contrary to our results, under α -interferon therapy, a background of atopy does not seem important although reported [22].

In conclusion, our study shows that a personal history of atopic symptoms is predictive of the occurrence of ec-

zema-like lesions in patients undergoing infliximab infusion. Our results suggest that atopic patients should be informed of the possibility of developing these symptoms, prompting the adoption of preventive strategies after the initial flare [23]. More recently, anti-TNF therapy has been proposed for the treatment of refractory asthma [24]. Such a target population is at risk of developing atopic-dermatitis-like lesions under such a treatment, given its high prevalence of atopy.

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