



Letter

Hypersensitivity reactions during treatment with infliximab, etanercept, and adalimumab

The recent development of biologic agents, namely, anti-tumor necrosis factor alpha (TNF α) agents, represents a major breakthrough for the treatment of immune-mediated disorders.¹ Available anti-TNF α agents neutralize TNF α in different ways.^{2–4} Given their structural and functional differences, distinct safety profiles can be expected for each of these agents. Among side effects, hypersensitivity reactions, including anaphylaxis, have been frequently reported.⁵ Thus, one must define simple and reliable diagnostic tests for these patients. Our aims are to analyze the frequency of hypersensitivity reactions to anti-TNF α agents and to evaluate the role of skin tests in the diagnosis.

In the Clinical Immunology and Rheumatology Units, Pisa University, 671 patients were treated with anti-TNF α agents (infliximab or etanercept or adalimumab) for autoimmune diseases (2000–2009). Among them, 51 patients experienced at least 1 hypersensitivity reaction to 1 or more anti-TNF α agents, defined as previously reported.⁶ Written consent was obtained from the patients according to the Helsinki's Declaration. The local ethical committee approved the study. Skin prick test (SPT) and intradermal injection were done with commercial anti-TNF α agents. Infliximab (SPT 10 mg/mL; intradermal 0.1, 1, 10 mg/mL) and adalimumab (SPT 40 mg/mL; intradermal 4, 40 mg/mL) concentrations were defined in 10 healthy subjects. Etanercept concentrations were previously reported (SPT 25 mg/mL; intradermal 0.1, 1, 5 mg/mL). Each patient has been tested for the 3 anti-TNF α agents.

Fifty-one patients of 671 experienced hypersensitivity reactions to anti-TNF α agents (26 rheumatoid arthritis, 8 spondyloarthritis, 8 psoriatic arthropathy, 5 ankylosing spondylitis, 2 Behcet's disease,

1 Still disease, 1 Crohn's disease). Patients' demographic and clinical characteristics are reported in Table 1. The culprit anti-TNF α agent was tested in 26 of 51 patients who developed hypersensitivity reactions and gave their informed consent to perform in vivo tests. Among the 8 patients with anaphylaxis to infliximab, 5 resulted positive to intradermal injection and 3 negative to SPT and intradermal injection. All 6 patients with urticaria/angioedema resulted positive to intradermal injection with infliximab. Among the 9 patients with reactions to etanercept (5 urticaria/angioedema and 4 local reactions), we observed positive intradermal injection with etanercept in 2 of 5 patients with urticaria/angioedema and 3 of 4 with local reactions. One of 6 patient with reactions to adalimumab (5 local reactions and 1 urticaria/angioedema) resulted positive to the intradermal injection with adalimumab.

Interestingly, 2 patients developed hypersensitivity reactions to all of the 3 agents. One resulted positive only to infliximab. The second, positive to all of the anti-TNF α , developed anaphylaxis with infliximab and large local reactions with etanercept and adalimumab.

In the current study, we report our experience on hypersensitivity reactions to 3 anti-TNF α agents in patients with systemic autoimmune diseases.

We observed the highest frequency and severity of reactions in patients treated with infliximab. In fact, the 60.8% of all the hypersensitivity reactions were attributable to infliximab, 25.5% to etanercept, and 11.7% to adalimumab. The most serious, anaphylaxis, was in 91.3% of cases attributable to infliximab. In contrast, anaphylaxis was observed in 2% of patients treated with etanercept and in no patient receiving adalimumab. The reactions to etanercept and

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Table 1
Characteristics of patients with hypersensitivity to anti-TNF α agents

	Infliximab	Etanercept	Adalimumab
Number of reactions/all treated patients	31/225 (13.8%)	13/245 (5.3%)	7/201 (3.5%)
Number of reactions/total reactions	31/51 (60.8%)	13/51 (25.5%)	7/51 (11.7%)
F/M	32/8	11/2	6/1
Mean of age (range)	46.3 (22–84)	55.7 (30–71)	54 (27–71)
Duration of the disease (mean of years)	14.4	17	15
Atopy in the reactions	6/31 (19.3%)	3/13 (23%)	1/7 (14.3%)
Atopy in treated patients	38/225 (16.9%)	50/245 (20.4%)	30/201 (14.9%)
Anaphylaxis/number of reactions	21/31 (67.7%)	2/13 (15.4%)	0/7 (0%)
Urticaria or angioedema/number of reactions	10/31 (32.2%)	5/13 (38.5%)	3/7 (42.8%)
Local reactions/number of reactions	0/31 (0%)	4/13 (30.7%)	3/7 (42.8%)
Other reactions (pruritus, morbilliform reactions, eosinophilia)/number of reactions	0/31 (0%)	2/13 (15.4%)	1/7 (14.3%)
IgE-mediated reactions/tested patients	11/14 (78.6%)	5/9 (55.5%)	1/6 (16.7%)
Non-IgE-mediated reactions/tested patients	3/14 (21.4%)	4/9 (44.5%)	5/6 (83.3%)

Abbreviations: F, female; M, male.

adalimumab were mainly local and mild. Of interest, a previous history of atopy had no predictive value on the development of any type of hypersensitivity reactions to these agents.

In drug hypersensitivity, anaphylaxis and urticaria are the clinical manifestations of mast cell-degranulation attributable to IgE-mediated or non-IgE-mediated mechanisms. The 2 mast cell activation pathways can be differentiated by identifying the IgE specific for the culprit drug. Recently, the detection of IgE anti-infliximab has been reported,⁷ but the assay has not yet been validated. In the diagnosis of reactions to anti-TNF agents as to any other drug, skin tests still represent the currently used tool to identify mast cell-sensitizing specific IgE. In fact, a correlation between serological IgE positivity and intradermal test results has been recently reported in patients with reactions to infliximab.⁸

In all cases of urticaria and in 5 of anaphylaxis out of the 8 observed, the skin tests resulted positive for infliximab, indicating an IgE-mediated response. Interestingly, the 3 patients with anaphylaxis and negative skin tests did not experience urticaria and developed the reaction at the first administration of the drug, suggesting a non-IgE-mediated anaphylaxis. On the contrary, all of the patients with positive skin tests to infliximab experienced clinical symptoms after the second infusion, suggesting a previous sensitization to this agent.

Infliximab is known to be more immunogenic than adalimumab: IgG anti-anti-TNF α are produced more frequently in patients treated with infliximab than with adalimumab and are responsible for treatment failures. According to our findings, infliximab is also responsible for induction of IgE and IgE-mediated responses, more frequently than etanercept and adalimumab.

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