

# Correlation between atopy and hypersensitivity reactions during therapy with three different TNF- $\alpha$ blocking agents in rheumatoid arthritis

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## ABSTRACT

**Objective.** The use of TNF- $\alpha$  antagonists (infliximab, etanercept, adalimumab) has changed the course of many rheumatic diseases including rheumatoid arthritis (RA). Since their approval, some questions regarding their safety have been raised. Both acute and delayed reactions have been described.

**Methods.** The aim of our work was to detect if there is a different incidence of hypersensitivity reactions – infusion reactions to infliximab or injection site reactions with etanercept or adalimumab – in atopic patients versus non-atopic patients.

In 90 patients (82 females, 8 males) with rheumatoid arthritis we evaluated, during the first year of therapy with three different TNF- $\alpha$  blocking agents, total serum IgE (normal value <100 KU/L) (method ImmunoCAP PHADIA) and serum specific IgE performing a qualitative multi-allergen test for inhalant allergens (PHADIATOP, method ImmunoCAP PHADIA). In all patients we evaluated injection site reactions (ISR) to etanercept and adalimumab – erythema, edema and itching at the site of subcutaneous administration – and infusion reactions to infliximab – hypotension/hypertension, chest pain, dyspnea, laryngospasm, fever, urticaria angioedema.

**Results.** We obtained the following results: patients with high value of total IgE were 15/90 (16.6 %), patients with total IgE in normal range were 75/90 (83.4.%), reactions in patients with high total IgE were 6.7% and in patients with normal total IgE were 18.7% ( $p=0.255$  ns). As regards serum specific IgE, patients with specific IgE were 17/90 (18.8%) patients without specific IgE were 73/90 (81.2%), reactions in patients with specific IgE were 11.8% and in patients without specific IgE were 17.8% ( $p=0.547$  ns). Also, when the data were divided for the three groups, the differences were not statistically significant.

**Conclusion.** Adverse reactions to biological agents have been categorized into five types. In hypersensitivity reactions – the  $\beta$  type reactions – an immune mechanism is suspected. Our

data showed that there was no correlation between the atopic status and the incidence of hypersensitivity reactions during the first year of therapy with three different TNF- $\alpha$  blocking agents.

## Introduction

Over 400,000 patients worldwide have been treated with tumour necrosis factor alpha antagonists (infliximab, etanercept, adalimumab) for indications that include rheumatoid arthritis (RA) and psoriatic arthritis (PA). Since their approval, some questions regarding their safety have been raised. Rare hypersensitivity reactions, both acute and delayed have been described (1).

Many reports showed reactions in patients receiving intravenous infliximab, a chimeric IgG1K antibody anti TNF- $\alpha$  (2). Immune-mediated side effects, among them various cutaneous reactions, have been encountered during therapy with TNF alpha blocking agents. A recent paper showed that for etanercept, injection site reactions occurred in 29.3% patients (3).

The aim of our work was to detect if there is a different incidence of hypersensitivity reactions during infliximab infusions or local injections with etanercept or adalimumab in atopic patients versus non atopic patients.

## Materials and methods

In a homogeneous group of 90 patients (82 females, 8 males) with rheumatoid arthritis during the first year of therapy with three different TNF- $\alpha$  blocking agents, we evaluated the level of total serum IgE by means of ImmunoCAP PHADIA – normal values less than 100 KU/L – and serum specific IgE by means of a qualitative multi-allergen test for inhalant allergens – Phadiatop, ImmunoCAP PHADIA.

Ninety patients were referred to the Rheumatology Unit of Nuovo Ospedale S. Giovanni di Dio (ASL10 Florence, Italy). After signing an informed consent (according to the Declaration of Helsinki), and obtaining the permission from the local ethics committee of ASL10 Florence, the patients participated in the study. Thirty-seven patients were in therapy with etanercept 50 mg/week, 27 patients were in therapy with

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infliximab 3 mg/kg every 8 week, 26 patients were in therapy with adalimumab 40 mg every other week. For all the patients we evaluated injection site reactions (IRS) to etanercept and adalimumab (erythema, edema and itching at the site of subcutaneous administration) and acute infusion reactions to infliximab (hypotension/hypertension, chest pain, dyspnea, laryngospasm, fever, urticaria angioedema). For all the patients an evaluation by the specialist of the Allergy and Clinical Immunology Unit was made. We evaluated the concomitant therapy with DMARD in all the patients (methotrexate/leflunomide), the mean daily dosage of corticosteroid drugs, and the disease activity with number of tender joints, number of swollen joints, global assessment and DAS28. Moreover, we also performed the determination of some acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for all the patients.

#### Statistical analysis

Data were analysed using SPSS 10.0 for Windows. Data were analyzed using  $\chi^2$  test with Yates's factor correction for percentage differences and Fisher's test for concordance evaluation. *P*-values less than 0.05 were considered to be of statistical significance.

#### Results

We obtained the following results (see Table I):

Patients with a high value of total IgE were 15/90 (16.6%), patients with total IgE in the normal range were 75/90 (83.4%). Reactions in the high total IgE group were 6.7%, reactions in the total IgE negative group were 18.7%  $p=0.255$  ns.

Patients with specific IgE were 17/90 (18.8%), patients without specific IgE were 73/90 (81.2%), reactions in patients with specific IgE were 11.8%; reactions in patients without specific IgE were 17.8%  $p=0.547$  ns.

When the results were divided for each drug group we obtained the following results:

**Etanercept group:** patients with a high value of total IgE were 11/36 (30.5%), patients with total IgE in the normal

**Table I.** Adverse reactions and total and specific IgE.

			Adverse reactions		Total
			No	Yes	
Global sample	Total IgE	Neg	61 (81.3%)	14 (18.7%)	75
		Pos	14 (93.3%)	1 (6.7%)	15
	Total		75	15	90
	Specific IgE	Neg	60 (82.2%)	13 (17.8%)	73
		Pos	15 (88.2%)	2 (11.8%)	17
	Total		75	15	90
Adalimumab	Specific IgE	Neg	18 (78.3%)	5 (21.7%)	23
		Pos	3 (100.0%)	0 (0.0%)	3
	Total		21	5	26
Etanercept	Total IgE	Neg	21 (84.0%)	4 (16.0%)	25
		Pos	10 (90.9%)	1 (9.1%)	11
	Total		31	5	36
	Specific IgE	Neg	22 (84.6%)	4 (15.4%)	26
		Pos	9 (90.0%)	1 (10.0%)	10
	Total		31	5	36
Infliximab	Total IgE	Neg	18 (78.3%)	5 (21.7%)	23
		Pos	4 (100.0%)	0 (0.0%)	4
	Total		22	5	27
	Specific IgE	Neg	19 (82.6%)	4 (17.4%)	23
		Pos	3 (75.0%)	1 (25.0%)	4
	Total		22	5	27

range were 25/36 (69.4%), reactions in patients with a high total IgE were 9.1%, reactions in patients with total IgE in the normal range were 16.0%  $p=0.581$  ns. Patients with specific IgE were 10/36 (27.7%), patients without specific IgE were 26/36 (72.3%). Reactions in patients with specific IgE were 10.0%, reactions in patients without specific IgE were 15.4%  $p=0.676$  ns.

**Infliximab group:** patients with a high value of total IgE were 4/27 (14.8%), patients with total IgE in the normal range were 23/27 (85.1%), reactions in patients with a high total IgE were 21.7%, reactions in patients with total IgE in the normal range were 0%,  $p=0.302$  ns. Patients with specific IgE were 4/27 (14.8%), patients without specific IgE were 23/27 (85.1%). Reactions in patients with specific IgE were 25.0%, reactions in patients without specific IgE were 17.4%  $p=0.718$  ns.

**Adalimumab group:** patients with specific IgE were 3/26 (19.2%), patients without specific IgE were 23/26 (88.4%), reactions in patients with specific IgE were 0%, reactions in patients without specific IgE were 21.7%  $p=0.369$  ns. Patients with total IgE in the normal range were 100%. Reac-

tions in patients with total IgE in the normal range were 3/26 (19.2%): a statistical evaluation was not possible due to the absence of a group with abnormal total IgE.

No correlation between hypersensitivity reactions and disease activity evaluated by DAS and DAS28 was found.

#### Discussion

In this paper we have focused on the role of atopic status and the incidence of hypersensitivity reactions during the first year of therapy with three different TNF- $\alpha$  blocking agents, but we have not observed statistically significant correlations.

Adverse reactions to biological agents were categorized into five types (4): in type  $\beta$  – hypersensitivity reactions – an immune mechanism was suspected: type I (specific IgE) or type III (specific IgG) or type IV (cell-mediated) following Gell and Coombs.

Infliximab is a 149 kDa chimeric immunoglobulin IgG1 anti-TNF- $\alpha$  antibody containing the antigen binding region of the mouse antibody. It can give acute infusion reactions that occur within 24h after administration, usually between 10 minutes and 4

hours. In RA, the frequency of acute infusions ranges from 5.8% (5) to 18% (6). The pathophysiology of acute infusion reactions remains unknown: in spite of several case reports of acute type  $\beta$  infusion reactions, serum specific IgE to infliximab has never been reported (7). It has been demonstrated that the concomitant administration of immunosuppressive drugs – methotrexate – reduces the rate of development of antibodies to infliximab and also the rate of infusion reactions, but the premedication with betamethasone does not decrease the incidence and the severity of infusion reactions in RA (8). The symptoms occurring from 24 hours to 14 days after the administration are suggestive for a serum sickness, a type III immuno-complex-mediated mechanism; the prognosis is excellent but it is possible to have an acute respiratory distress syndrome (9).

A recent paper showed that no difference in the prevalence of infusion reactions has been observed in patients treated with 3 versus 5 mg/kg. A possible difference in the number of infusion reactions has been attributed to the time of infusion and to the different diseases (rheumatoid arthritis or spondyloarthropathies) were a different percentage of ANA positivity at baseline could be a predictor factor for infliximab reactions (10).

Etanercept is a 150KDa soluble TNF- $\alpha$  receptor protein composed of two dimers, each with an extracellular, ligand binding portion of higher affinity type 2 TNF- $\alpha$  receptor (p75) linked to the Fc portion of human IgG1. Injection site reactions may appear within 24–48 hours and last 3–5 days. The incidence in RA varies from 20% (11) to 45% (12). These patients usually have a good response to treatment with etanercept. Forty percent of these patients also developed a “recall ISR” that is a similar reaction in the site of previous injections (11). Histological findings on skin biopsies showed a T cells dependent allergic reaction but an eosinophilic cellulitis-like reaction with Th-2 mediated phenomenon is also reported (13). Allergological skin tests such as prick intradermal or patch tests are not reported in the literature.

We observed in our two patients with ISR during etanercept therapy, after intradermal test with a commercial preparation, a positivity at the immediate reading (20 minutes), suggestive of an immediate allergic reaction, possibly IgE mediated (14). Antibodies to etanercept are found with a much lesser frequency than for infliximab with a percentage of 5.6% and do not seem to correlate with ISRs or reduced activity (3).

Adalimumab is a 148kDa recombinant human high affinity IgG1 monoclonal antibody against TNF- $\alpha$ , preventing cytokine binding to its receptor and lysing cells that express TNF- $\alpha$  on their surface. ISRs to adalimumab are rare with a percentage from 6.6%(15) to 15.3%(16). We observed intradermal tests in patients with ISR during therapy with adalimumab positive at immediate reading in one patient, and at delayed reading in a second patient, lasting 3–5 days, with patch test negative (14). Systemic reactions such as dyspnea (17) or urticaria-angioedema (18, 21–22) are rarely described. The review of the literature showed that hypersensitivity reactions to TNF- $\alpha$  blocking agents are not uncommon. These manifestations should be considered in a first hypothesis as a type  $\beta$  reaction IgE-mediated against this antigen or a delayed reaction mediated by IgG and complement (4). In a second hypothesis, a  $\gamma$ -reaction is possible: anti-TNF- $\alpha$  induces a cytokine imbalance with a predominance of phenotype Th2 with induction of a vasculitis-like (19), allergic disease like asthma (17) atopic dermatitis and allergic drug reaction (20). This mechanism could be activated because of a switch from Th1 to Th2 in patients with autoimmune diseases but is not due to the atopic status of the patient.

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