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Original article

Increased prevalence of allergic sensitisation in rheumatoid arthritis patients treated with anti-TNFα

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Abstract

Introduction. – Tumour necrosis factor alpha (TNFα) has emerged as a therapeutic target in chronic inflammatory disorders characterised by a Th1 type immune response, such as rheumatoid arthritis (RA). The presence of allergic disease in these patients could be influenced both by the presence of RA and anti-TNFα therapy. Our aim was to evaluate the prevalence of sensitisation to airborne allergens and allergic disease in RA patients, with and without anti-TNFα treatment.

Methods. – RA patients with ($N = 20$) and without ($N = 20$) anti-TNFα therapy (groups T and R) were enrolled. Healthy controls ($N = 60$, group C) were randomly selected from the general population. All participants answered a standardised questionnaire to assess the prevalence of allergic disease and had skin prick tests (SPT) with a standard panel of airborne allergen extracts.

Results. – Significant differences were found in the prevalence of positive SPT between groups T and R (70% vs 35%, $p = 0.027$) and groups T and C (70% vs 36.7%, $p = 0.009$), but not between groups R and C. The prevalence of allergic disease was similar in the three groups. Groups T and R had similar gender and age distribution, disease duration, disease activity score (DAS28), erythrocyte sedimentation rate and serum C-reactive protein.

Conclusions. – Increased prevalence of sensitisation to airborne allergens in RA patients treated with anti-TNFα was found. The clinical impact of the positive SPT following anti-TNFα initiation has now to be assessed.

Keywords: TNFα; Rheumatoid arthritis; Autoimmunity; Atopy; Allergy

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder whose underlying cause is still unclear. T cell involvement in the pathogenesis of RA is unquestionable. Their role is demonstrated by the presence of activated CD4 + and CD8 + T cells in the synovial fluid and lining tissue of RA inflamed joints [1].

Until recently, the adaptative cellular immune response has been characterized broadly by two functional subsets of CD4 + T cells, which can be distinguished according to their cytokine secretion profiles [2]. Each subset, T helper type 1 (Th1) and T helper type 2 (Th2), regulates the other in a dynamic process. Different disease manifestations are associated with prominence of one or the other of Th1 or Th2 phenotypes [3]. RA is generally thought to be a Th1 disease, T cell clones from synovium or peripheral blood having a Th1-like phenotype [4]. T cells from joints affected by RA produce large amounts of IFN-γ but very small amounts of interleukin (IL)-4, and synovitis is associated with lack of the IL-4 gene [5,6]. Atopy, defined as a genetic propensity to develop IgE antibodies in response to specific allergens, results from a Th2 type response, with T cells producing the IgE-switching cytokines IL-4 and IL-13 [7]. Atopy can be assessed by skin prick tests (SPT) or determination of serum specific IgE. It is a well-established risk factor for allergic diseases, such as asthma, rhinitis and atopic eczema [8].

Tumour necrosis factor alpha (TNFα) is a pleiotropic cytokine that has emerged as a therapeutic target in chronic inflammatory disorders characterised by a Th1 type immune response, such as RA, in which TNFα is generated in excess [9].

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TNFα belongs to a family of peptide ligands that activate a corresponding set of structurally related receptors [10]. It is produced by several pro-inflammatory cells (mainly macrophages, but also monocytes, dendritic cells, B cells, CD4 + T cells, neutrophils, mast cells and eosinophils) and structural cells (fibroblasts, epithelial cells and smooth muscle cells). It is an important cytokine of the innate immune response, but its biological function also includes the modulation of growth differentiation and proliferation of a variety of cell types and it is also important in apoptosis [11]. Besides these effects, TNFα is a well-known inducer of the inflammatory response and a regulator of immunity. Its inflammatory properties are classically mediated by means of a wide variety of pro-inflammatory cytokines, including IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, interferon gamma (IFN-γ) and transforming growth factor-β (TGF-β), generated mainly through nuclear factor κB (NF-κB) activation [11].

The development of Th2 type disorders in RA patients treated with anti-TNFα agents could therefore be influenced not only by the presence of RA but also by the anti-TNFα therapy itself. We conducted a case–control study to evaluate the prevalence of sensitisation to airborne allergens and allergic disease in RA patients, with and without anti-TNFα treatment, and in healthy controls. Our results demonstrate, for the first time, an increased prevalence of sensitisation to airborne allergens in RA patients treated with anti-TNFα.

2. Methods

2.1. Patients

This case-control study was conducted between July and December 2007 and enrolled 20 RA patients with anti-TNFα therapy and 20 RA patients without anti-TNFα therapy, consecutively observed in the Rheumatology Department. RA was defined according to the American College of Rheumatology (formerly, the American Rheumatism Association) revised criteria. Disease activity score (DAS28) [12], erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), disease duration and current treatment (including dosages and duration of therapy) were recorded. Eosinophil peripheral blood count (Eos) and serum total IgE (IgE) were determined in all RA patients. IgE (UI/L) was determined using the nephelometry technique. Healthy controls ($N = 60$) were randomly selected from the general population. Informed consent was obtained from all patients and controls previously to enrolment.

2.2. Questionnaire

All patients and controls answered a standardised questionnaire validated in Portuguese to assess the prevalence of allergic disease [13]. The allergic disorders considered in the questionnaire were asthma, allergic rhinitis and atopic eczema, although it included a final broad question on any kind of diagnosed allergic disease, namely food, drug and venom allergy. The positive answers were systematically checked with a detailed clinical history by the same investigator (AS). Prevalence concerned only those subjects with clinical symptoms at the time or in the previous 12 months of the study.

2.3. Skin prick testing

All patients and controls underwent SPT with a standard panel of airborne allergen extracts, which included the Ga2len Pan-European Standard SPT Panel [14]. SPT were performed with a standardised procedure, on the volar surface of the non-dominant side forearm. Saline 0.9% was used as a negative control and histamine (concentration of 10 mg/ml of saline) was used as a positive control. SPT results in all patients and controls were assessed by one of two experienced blinded allergy nurses 15 minutes later. Weal diameters were measured as the mean of two perpendicular diameters including the widest one. A weal diameter greater or equal to 3 mm as opposed to the negative control was considered a positive result.

2.4. Statistical analysis

Descriptive characteristics of the study population were tabulated as median and interquartile range, or proportions as applicable. Groups T, R and C were statistically compared using Kruskal-Wallis, Mann-Whitney U and Chi^2 tests, as appropriate. Significance was determined using a two-sided α level of 0.05. Statistical analysis was performed using SPSS 14.0 for Windows.

3. Results

Our study population included 20 RA patients with anti-TNFα therapy (group T – 13 patients treated with 3 mg/kg of infliximab every eight weeks, five with 40 mg of adalimumab every two weeks and two with 50 mg of etanarcept every week), 20 RA patients without anti-TNFα therapy (group R) and 60 healthy controls (group C). Table 1 summarizes the descriptive characteristics of the patients study cohort, according to the treatment group. Comparing groups T and R, there were no statistically significant differences in gender and age distribution, duration of the disease, DAS28, ESR or CRP.

All patients were taking doses of prednisolone less than or equal to 7.5 mg per day (or equivalent). Although there were no differences regarding the proportion of patients taking prednisolone and methotrexate, the dosages of both medications were higher in group R compared to group T. In group R, there were significantly more patients on hydroxychloroquine and sulfasalazine. Median (IQR) anti-TNFα therapy duration in group T was 24.5 (9.75–46.5) months.

Table 2 compares groups of RA patients and controls regarding age, prevalence of allergic disease, proportion of participants with positive SPT, Eos and serum total IgE. A higher prevalence of positive SPT was found in group T compared to group R ($p = 0.027$, Chi^2) and in group T compared to group C ($p = 0.009$, Chi^2). There were no differences in the prevalence of positive SPT when comparing groups R and C ($p = 0.893$, Chi^2). The prevalence of allergic disease according to the questionnaire was similar in the three groups. No differences were found

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Table 1
Summary and comparison of the RA descriptive characteristics of the study cohort according to the treatment group ($n = 40$).

	RA patients with anti-TNFα (group T, $n = 20$)	RA patients without anti-TNFα (group R, $n = 20$)	p-value
Age – years, median (IQR)	54.50 (50.25–61.50)	58.00 (42.25–69.75)	$p = 0.189$
Gender – female, n (%)	18 (90.00)	17 (85.00)	$p = 1.000$
Disease duration – years, median (IQR)	10.00 (6.50–15.00)	17.00 (4.75–20.00)	$p = 0.355$
DAS28 – median (IQR)	3.07 (2.41–4.18)	2.57 (1.67–3.36)	$p = 0.142$
ESR (mm/1h) – median (IQR)	15.00 (7.75–42.75)	13.00 (8.00–26.75)	$p = 0.565$
CRP (mg/dl) – median (IQR)	0.5 (0.36–1.10)	0.72 (0.43–1.93)	$p = 0.383$
Current medication – n (%)			
Prednisolone	15 (75.00)	16 (80.00)	$p = 0.705$
Methotrexate	15 (75.00)	18 (90.00)	$p = 0.212$
Sulfasalazine	1 (5.00)	8 (40.00)	**$p = 0.008$**
Hydroxychloroquine	2 (10.00)	13 (65.00)	**$p < 0.001$**
Current dose of medication – median (IQR)			
Prednisolone (mg/day)			
Methotrexate (mg/week)	3.75 (0.63–5.00)	5.00 (5.00–7.50)	**$p = 0.039$**
Sulfasalazine (g/day)	10.00 (1.88–21.88)	22.50 (11.25–25.00)	**$p = 0.040$**
Hydroxychloroquine (mg/day)	0.00 (0.00–0.00)	0.00 (0.00–2.00)	**$p = 0.014$**
	0.00 (0.00–0.00)	400.00 (0.00–400.00)	**$p < 0.001$**

IQR: interquartile range.
Mann-Whitney U test (quantitative variables) and Chi^2 test (qualitative variables) were used.

between groups T and R concerning Eos or IgE. Controls had a similar gender distribution ($p = 0.058$, Mann-Whitney U) but younger age than groups T ($p < 0.001$, Mann-Whitney U) and R ($p < 0.001$, Mann-Whitney U).

4. Discussion

An increased prevalence of sensitisation to airborne allergens in RA patients treated with anti-TNFα was found, suggesting that pharmacological attenuation of RA with anti-TNFα may predispose to atopy.

To our knowledge no similar studies in RA patients treated with anti-TNFα have been performed. This is the first observation of such finding and is consistent with previous reports of atopic dermatitis following anti-TNFα therapy for RA [15,16] and psoriasis [17]. Also consistent with our report are the fact that Th2 cells down-regulate IL-1 and TNFα in a variety of experimental conditions [18-20], studies in animal models suggesting that Th2 cytokines attenuate Th1-dependent autoimmune disorders[21-23] and published data suggesting that a Th2 response protects against or limits the development of Th1 autoimmune conditions [24,25]. Sensitisation to airborne allergens, as shown by positive SPT, is an evidence of atopy and is associated with an increased risk of allergic disease over time [8].

We did not find any difference in the prevalence of allergic disease when comparing RA patients with and without anti-TNFα therapy and controls. The prevalence of positive SPT was also similar between RA patients without anti-TNFα therapy and controls. These results are consistent with the study of O'Driscoll et al. [26], who found a similar incidence of atopy, as determined by history or SPT, when comparing 40 subjects with RA to age-matched controls. They also found that two of 266 atopic subjects followed in an allergy clinic had RA, a prevalence rate similar to that of RA in the general population. Similarly, Hassan et al. [27], studying 100 patients with RA and 50 controls, also reported no differences between the groups in atopy as assessed by SPT. Olsson et al. [28] found no clear asso-

Table 2
Comparison between groups of RA patients and controls regarding age, prevalence of allergy, positive SPT, eosinophil peripheral blood count (Eos) and serum total IgE (IgE).

	RA patients with anti-TNFα (group T, $N = 20$)	RA patients without anti-TNFα (group R, $N = 20$)	Controls (group C, $N = 60$)	p-value
Age – years, median (IQR)	54.50 (50.25–61.50)	58.00 (42.25–69.75)	36.00 (28.25–44.75)	**< 0.001**
Gender – female, N (%)	18 (90.00)	17 (85.00)	40 (66.70)	0.058
Prevalence of allergic disease – N (%)	11 (55.00)	7 (35.00)	22 (36.70)	0.307
Positive SPT – N (%)	14 (70.00)	7 (35.00)	22 (36.70)	**0.024**
Eos – per mm 3, median (IQR)	165.00 (97–296.25)	139.00 (87.50–180)	NP	0.229
IgE – U/ml, median (IQR)	18.00 (18.00–65.75)	18.00 (18.00–18.00)	NP	0.242

NP: Not performed; IQR: interquartile range.
Kruskal-Wallis test (quantitative variables, when comparing three groups), Mann-Whitney U test (quantitative variables, when comparing two groups) and Chi^2 test (qualitative variables) were used.
Elements is bold represent statistical significant values.

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ciation between RA and atopy in a study with 263 cases and 541 controls based on data from a postal questionnaire followed by determination of serum specific IgE to common allergens, although the same authors found a trend towards a decrease in atopic disease in patients with RA in a previous retrospective study which included 282 cases and 507 controls [29].

In contrast, two questionnaire-based studies suggested a lower prevalence of self-reported atopy in cohorts of RA patients. Hilliquin et al. [30] compared 173 consecutive RA patients to age and sex-matched controls and found, irrespective of treatment for RA, a decreased cumulative incidence and point prevalence of atopy. Rudwaleit et al. [31] analysed 728 subjects with RA from the database of a university outpatient clinic and 900 controls comprised of a combination of hospital staff members and elderly patients with osteoporosis. In this study, the prevalence of atopic disorders globally and allergic rhinitis in particular was decreased in the RA subjects. Interestingly, a subanalysis of the data found lower severity of RA among those subjects who presented with atopic disease prior to the onset of RA compared to patients in whom RA preceded the atopic disorder.

The studies by Hilliquin et al. [30] and Rudwaleit et al. [31] are supported by a Dutch retrospective cohort study from Verhoef et al. [32] which showed that the prevalence of allergic rhinitis in RA patients was about half of that in controls. Furthermore, RA was less severe in patients suffering also from allergic rhinitis than in RA patients without allergic rhinitis, suggesting that atopy affects not only the incidence but also the severity of RA. In this study, peripheral blood mononuclear cells from patients with both diseases secreted less IFN-γ in vitro during pollen season than the corresponding cells of patients with RA but no allergic rhinitis. Once the pollen season was finished, the levels of IFN-γ were similar in the two groups of patients. In summary, despite their limitations, these studies suggest that atopy is decreased in patients with RA compared to controls and that among those patients with both diseases, the severity of RA is decreased.

Demographic characteristics in the two RA patients' groups (groups R and T) were similar, namely age and gender distribution, disease activity and inflammatory markers, supporting their similarity except for the anti-TNFα therapy. However, our results must be interpreted in the light of a few limitations. Our main objective was to compare the prevalence of sensitization to airborne allergens and allergic disease in patients with and without anti-TNFα treatment; as this prevalence has never been selectively reported in these two subgroups of RA patients, sample size calculation could not be performed. However, taking into account the reported prevalence of allergic disease in the RA population as a whole and in healthy controls, our sample may have been too small and possibly underpowered to detect significant differences. The differences regarding sulfasalazine and hydroxychloroquine were predictable, since the majority of RA patients withdrew these drugs once they started anti-TNFα therapy. Methotrexate and prednisolone could have influenced the results, although given the small differences between groups R and T regarding the dosage and the low doses of prednisolone (all patients receiving less than or equal to 7.5 mg/day, a widely accepted inferior cut-off for the immunosuppressive effect of corticosteroids [33]), we do not consider these differences to represent a major limitation.

The controls were randomly selected, without a matching procedure designed to prevent factors, such as age, occupation and environment, from affecting the expression of atopy, and that could have represented a selection bias. However, despite birth cohort [34] and longitudinal [35] studies showing an increase in allergic sensitisation and symptoms overtime in a considered group of people, in cross-sectional studies the prevalence of allergic diseases has been described as being lower in older people [36]. The controls in our study were younger than cases; therefore, the influence of this factor may have been minor. Supporting the validity of our control group is the fact that the prevalence of atopy and allergic disease, as assessed by the SPT and questionnaire, was similar to that reported in the general population [37,38].

Recent observations challenge the validity of the long-standing Th1/Th2 paradigm [39]. Additional lymphocyte subsets, such as Th17 cells and regulatory T cells, as well as novel soluble factors have been recognised, providing a new prism through which to examine the intersection of autoimmune and allergic disease [40]. Still, in a recent review of the epidemiological and mechanistic literature about the nexus between atopic disease and autoimmunity, Rabin and Levinson [41] presented a model whereby active Th1 inflammation may suppress the development of atopy, and atopy may suppress the severity but not necessarily the onset of autoimmunity. These authors also draw our attention to the fact that this discussion may help to predict or interpret unexpected consequences of novel agents used to target autoimmune or atopic disorders, i.e. therapies targeting Th1- or Th2-specific responses may trigger or reveal underlying atopy or autoimmunity respectively.

Finally, there are differences from the molecular point of view and the mechanisms whereby each different anti-TNFα drug acts are not entirely equal [9]. Infliximab is a chimeric monoclonal antibody and adalimumab is a human recombinant monoclonal IgG_1 antibody; they bind both to soluble and membrane-bound TNF. Etanercept, a fusion protein consisting of the extracellular ligand of the p75 TNFα receptor combined with the Fc portion of human IgG_1, binds soluble and, to a lesser degree, membrane-bound TNF and also lymphotoxin-α (TNF-β). Although infliximab binds both monomeric and trimeric (bioactive) TNFα, it is postulated to cause cell lysis via antibody-dependent, cell mediated cytotoxicity or via complement activation. In our study only two patients were treated with etanercept. The use of different anti-TNFα drugs should be taken into account in future studies about the prevalence of atopy in anti-TNFα treated patients. The biologic effects of the soluble receptor construct and monoclonal antibodies may not be the same, as demonstrated by the higher incidence and earlier occurrence of tuberculosis with infliximab and adalimumab than with etanercept, or by the lack of efficacy of etanercept in granulomatous diseases, such as Crohn's disease, Wegener's granulomatosis and sarcoidosis (with a possible triggering effect for the last).

In summary, an increased prevalence of sensitisation to airborne allergens in RA patients treated with anti-TNFα was

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found, suggesting that pharmacological attenuation of RA with anti-TNFα may predispose to atopy. The clinical impact of the positive SPT following anti-TNFα initiation has now to be assessed.

Further studies are required to clarify the relationship between RA, atopy and anti-TNFα therapy, and to identify the factors, namely the genetic background, environmental factors, novel soluble factors and additional lymphocyte subsets (such as Th17 cells and Tregs) [39-41] affecting the expression of RA and atopy. In the future, as clinical testing of selective therapies for autoimmune disorders progress towards larger trials, it would be prudent to monitor for manifestations of atopy and continue post-marketing monitoring of currently and futurely licensed biologic drugs.

Conflicts of interest

None of the authors has any conflicts of interest to declare.

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