Th2-mediated atopic disease protection in Th1-mediated rheumatoid arthritis

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ABSTRACT

Objective. The balance between CD4⁺ T-helper (h) cell subsets (Th1 and Th2) plays an important role in the pathogenesis of rheumatoid arthritis (RA) and atopy. While RA is believed to be a Th1-mediated disease, Th2 cells predominate in atopic disorders. The purpose of this study was to investigate differences in the occurrence of allergy, hay fever, house dust mite sensitivity and asthma, as well as total serum IgE levels in RA patients and controls.

Methods. The case history of atopic disorders was assessed in 134 RA patients and compared to those found in 305 healthy blood donors. RA patients also answered clinical questions concerning disease activity and severity. Total serum IgE levels were measured in both groups, taking into consideration disease modifying therapy.

Results. A significantly lower occurrence of medical history of hay fever (2.3%) and house dust mite sensitivity (3.1%) was found among RA patients compared to controls (24.2% and 12.2%, respectively; p < 0.0001 and p < 0.003 respectively). Moreover, RA patients had significantly lower total serum IgE levels than control subjects (p < 0.0001). RA was less severe in patients with atopy compared to non-atopic RA patients.

Conclusion. These results support the concept that RA and atopy antagonize each other and that a change in the cytokine patterns of Th1 and Th2 cells could provide an indication for curative effects on RA.

Key words: Rheumatoid arthritis, atopy, IgE, Th1, Th2, DMARD.
RA patients were 27.6% men and 72.4% women with a mean disease duration of 10 years (0.08–43 years). 60.4% of the RA patients were rheumatoid factor positive, 38.8% did not produce autoantibodies, and 0.7% had inconsistent results with regard to autoantibody production. Concerning disease modifying antirheumatic drug (DMARD) therapy, 33.8% (n = 48) of the RA patients were not taking DMARDs, while the majority were under DMARD treatment: 54.9% (n = 78) took methotrexate, 2.8% (n = 4) were on azathioprine and 2.8% (n = 4) took cyclosporine A + methotrexate. 83.5% (n = 112) RA patients were treated with corticosteroids.

The control group consisted of 305 healthy blood donors (matched for gender to the group of RA patients). Inclusion criteria for the control subjects was the condition that they were healthy blood donors with a minimum age of 18 years. Controls were required not to have had a desensitization nor to be the next of kin of any other control group member (exclusion criteria).

The study was approved by the local ethics committee. All participants were enrolled after they had given informed consent. Total serum IgE levels were measured in both groups by means of immuno nephelometry.

All individuals (controls and RA patients) were assessed by a physician-administered questionnaire for a medical history of hay fever, house dust mite allergy and asthma. This questionnaire has been validated by our group recently (23). Only unambiguous answers (yes or no) were assessed.

The occurrence of atopic disorders and the total serum IgE levels among RA patients were compared with those of the control group, and the disease severity of RA patients with atopy was compared to those who did not suffer from atopic disorders. RA patients were divided in two groups according to the Steinbrocker classification (22): group 1 had mild RA (Steinbrocker classification 1-2) and group 2 had severe RA (Steinbrocker classification 3-4). Statistical analysis was performed by means of the two-tailed chi-square test (occurrence of atopic disorders) and the two-tailed Mann-Whitney U test (total serum IgE levels). Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

**Results**

**Reduced incidence of atopy case history in RA patients**

A significantly lower occurrence of a case history of and risk for hay fever could be shown in RA patients. Only 2.3% of the RA patients reported a medical history of hay fever whereas 24.2% of the control group reported these complaints (p < 0.0001; OR 0.111; 95% CI 0.036 – 0.339). Occurrence of house dust mite sensitivity was significantly lower in RA patients as well. Only 3.1% of the RA patients, compared to 12.2% of the control group, had a positive medical history of house dust mite sensitivity (p = 0.003), which yields a relative risk (OR) of 0.310 (95% CI 0.121 – 0.793) for RA patients to develop an allergy to house dust mites. Concerning asthma no significant differences could be identified between the groups. 15 blood donors (5%) and 7 RA patients (5.3%) reported asthmatic complaints (p = 0.887; OR 1.047; 95% CI 0.558 – 1.964).

**Atopy case history and RA severity**

We further investigated the question of whether RA was less severe in RA patients with atopy than in patients who did not suffer from allergic disorders. Although the differences between patients with or without atopy were not statistically significant, they nevertheless show a trend towards a higher occurrence of allergies in patients with a mild form of RA than in patients with severe RA. 23.6% of the patients with mild RA reported a case history of allergies in comparison to 16.1% of the patients with severe RA.

**Total serum IgE levels are reduced in RA patients**

RA patients had significantly lower total serum IgE levels than controls (a median of 21.10 IU/ml vs. a median of 40.40 IU/ml, respectively). Figure 1 shows the 95% CI of total serum IgE levels in RA patients and controls. RA patients had a mean IgE level of 51.44 IU/ml, whereas control subjects had significantly higher IgE levels (mean 109.80 IU/ml; Mann-Whitney U test, p < 0.0001). The control and experimental subject data were then divided into one of two groups based on their IgE levels: low IgE (IgE levels ≤ 100 IU/ml) and high IgE (IgE levels > 100 IU/ml).

Only 11.9% of the RA patients had high IgE levels, whereas 25.7% of the control subjects had IgE levels > 100 IU/ml (chi-square test, p = 0.001, Table I). These result also remained highly significant when atopic RA patients as well as atopic controls were excluded from the calculations. It might be argued that reduced IgE levels in RA patients are simply due to treatment with corticosteroids or methotrexate. As shown in Table II, total IgE levels did not correlate with the doses of cortisone. With respect to methotrexate, IgE levels were reduced in RA patients taking methotrexate when compared to RA patients without methotrexate (mean IgE 33 IU/ml vs. 62 IU/ml; Mann-Whitney U test, p = 0.02). However, this result does not explain the principal differences in IgE levels between controls and RA patients since the RA group without methotrexate treatment still showed significantly reduced IgE levels in comparison to healthy controls (mean IgE 62 IU/ml vs. 109 IU/ml; Mann-Whitney U test, p = 0.016).

**Discussion**

The importance of the Th1/Th2 balance for autoimmune Th1-predominated...
diseases (such as RA) and Th2-mediated diseases (such as atopy) has been elucidated in several recent studies (11-14, 15-18). We hypothesized that RA and atopy counterbalance each other and that a concomitant occurrence of the diseases could lead to a diminished disease severity of both. As expected we could show a significantly lower occurrence of a medical history of hay fever and house dust mite sensitivity in RA patients compared to healthy controls.

The fact that there were no significant differences between RA patients and controls concerning the occurrence of asthma could have many reasons. While a medical history of atopic disorders like hay fever and house dust mite sensitivity can be reliably assessed by means of a questionnaire (because they have typical symptoms and occur during typical seasons) (23), asthma is more difficult to assess in this manner. Furthermore, there are different etiologic pathways for asthma (24) such that non-atopic forms of asthma could have skewed the results and the overall prevalence of asthma is low. The occurrence of atopy in the control group corresponds to the prevalence of atopic diseases in the general population, which is estimated to be at least about 20% (17, 24).

There are three studies supporting the antagonism of RA by atopy (and vice versa), which all discuss the Th1/Th2 counterbalance as the main mechanism responsible for the lower prevalence of atopy in RA patients. A rather clinically focused study (16) showed a reduced incidence and prevalence of atopic disorders in RA patients compared to matched controls but leaves the question open as to whether disease modifying therapy of RA patients or any illnesses or drugs in the control patients could have influenced the results. The second study (17) additionally included cytokine analysis, but was confined to the prevalence of hay fever only and did not investigate the possible influences of any drugs on the overall results either. The third study in favour of the Th1/Th2 counterbalance also showed a reduced prevalence of atopic disorders in RA patients (18), but again the differences were related neither to age nor to drugs.

In our study we not only investigated the occurrence of a medical history of hay fever in RA patients and controls, but the occurrence of house dust mite sensitivity and asthma as well. Moreover we measured total serum IgE levels in both groups as a biochemical parameter and related our results to the dimension of the disease and DMARD therapy of RA patients. To our knowledge this study is the first to show a significantly lower occurrence of atopic disorders and significantly lower levels of total serum IgE in RA patients compared to healthy controls, and above all it correlates the results to disease severity and disease modifying therapy.

Interestingly, there are also contradictory studies that argue against a Th1/Th2 counterbalance or any protective effects of Th1-mediated diseases on Th2-mediated disorders or vice versa. One study published in 2001 even showed a significantly higher cumulative incidence of Th2-mediated asthma in children who also suffer from a Th1-mediated disease such as coeliac disease, insulin dependent diabetes mellitus or RA (19). Another study, published in 2002, also questions the hypothesis of a mutual antagonism between RA and atopy (20). Further data against a Th1/Th2 antagonism were published in 1985 (25) – no differences in the prevalence of atopy could be found between RA patients and controls. Whether these findings (still) apply to the present circumstances is questionable, since a group of only 40 RA patients may be too small to accurately represent the population of RA patients and the prevalence of atopic disorders has been reported to be on the rise (24,26,27). The increasing prevalence of atopy is thought to be based on changes in lifestyles and living conditions (27, 28), family size/number of siblings (26, 29), a decrease in the incidence of infectious diseases in childhood (26, 29, 30), and increased exposure to cigarette smoke and pollutants (31,17). It can thus be presumed that the incidence of RA as a counterpart of atopy should decrease, for which evidence has arisen (32-34).

In RA as well as in atopy, both genetic predisposition and environmental factors play an important role. It follows now to question whether these factors can be influenced by Th1/Th2 antagonism and whether protective or curative effects result from it. Several studies have investigated this question (11,13, 34) and at least partly show some protective and inhibiting effects on Th1 mediated diseases by Th2 cytokines. However, it seems to be necessary to
influence the Th1/Th2 balance at an early stage in order to succeed in inducing a cytokine switch (11). To what extent these experimental findings are transferable to humans and whether there are risks in transferring cytokines or changing cytokine patterns still remain to be investigated.

This study shows that there is a reduced occurrence of atopic diseases as well as lower total serum IgE levels in RA patients compared to controls, suggesting that atopy as a Th2-predominated disease could protect against Th1 mediated diseases such as RA. In what way influences on the Th1/Th2 balance could be useful for protective or curative effects in RA is an important question still to be answered.

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