Clinical and Experimental Rheumatology 2003; 21: 481-484.



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

A.-D. Hartung[1], A. Bohnert[1], H. Hackstein[1], A. Ohly[1], K.L. Schmidt[2], G. Bein[1]

*[1]Institute of Clinical Immunology and Transfusion Medicine, Justus-Liebig-University Giessen; [2]Kerckhoffklinik Bad Nauheim, Germany*

*Cand.med. A.-D. Hartung (medical student); Dr. med. A. Bohnert, Research associate; Dr. med. H. Hackstein, Research associate; Cand.med. A. Ohly (medical student); Prof. K.L. Schmidt, Chair for Rheumatology, Physical Medicine & Balneology, University of Giessen; Prof. G. Bein, Director of the Institute of Clinical Immunology and Transfusion Medicine, University of Giessen.*

*Please address correspondence and reprint requests to: Prof. Dr. G. Bein, Institute of Clinical Immunology and Transfusion Medicine, Justus-Liebig-University Giessen, Langhansstrasse 7, 35392 Giessen, Germany.*
*E-mail: gregor.bein@immunologie.med.uni-giessen.de*

*Received on November 26, 2002; accepted in revised form on March 7, 2003.*



**Key words:** Rheumatoid arthritis, atopy, IgE, Th1, Th2, DMARD.

**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.*

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease of unknown (poly-)etiology and only partly known pathogenesis. As a systemic disease RA does not only affect the joints but can also involve other organs. The estimated prevalence of RA in western Europe and the United States is about 0.5% - 1% (1). As a strong association between HLA-DR4 (and HLA-DR1) and RA has been found, it is likely that there is a genetically determined susceptibility to RA, which has been investigated in several recent studies (2-8). However, environmental influences such as bacterial or viral infections also seem to be of importance for disease induction (9, 10).

$CD4^+$ T-helper (h) cell subsets, designated Th1 or Th2 cells according to their cytokine secretion profile, play a crucial role in the pathogenesis of many autoimmune diseases (11-14). Th1 cells, which produce predominantly IFNγ and TNFα, have been found to be antagonistic to Th2 cells, which secrete mainly IL-4 and IL-5 (11). Th1 cells are involved in the protection against intracellular parasites and delayed-type hypersensitivity, but they can cause autoimmune diseases such as rheumatoid arthritis and diabetes (11-13). Th2 cells, on the other hand, protect against metazoan parasites, for example, but also can induce atopic disorders resulting in high IgE levels or idiopathic hypereosinophilic syndromes (11, 12). Generation of Th1 cells is antagonized by IL-4 or IL-6, while IFNγ inhibits the proliferation of Th2 cells (11). Thus it is reasonable to conjecture that a Th2 response (e.g., an allergic/atopic disorder) could antagonize a Th1-mediated autoimmune disease like RA (or vice versa) (11,13,15-20).

The purpose of this study was to investigate the occurrence of a case history of allergy, hay fever, house dust mite sensitivity or asthma and total serum IgE levels in RA patients compared to healthy blood donors. In addition, the clinical history of the patient's RA (disease severity, autoantibody production, ESR, CRP, smoking habits, concomitant diseases, medication) was taken into consideration.

## Patients and methods

134 consecutive outpatients diagnosed with RA according to the revised American Rheumatism Association criteria (21) were assessed regarding sex, age of RA onset, medication, and disease severity according to the classification of Steinbrocker (22). Inclusion criteria were the unequivocal fulfilment of the American Rheumatism Association criteria and a minimum age of 18 years. Exclusion criteria were first degree kinship in the group of RA patients, pregnancy and anaemia.

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 cyclosporineA + methothrexate. 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 immunonephelometry.

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-Whithney 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).

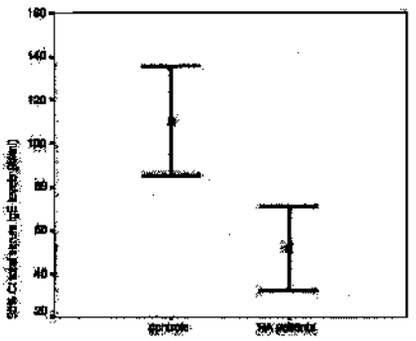

**Fig. 1.** Total serum IgE levels (mean ± 95% confidence interval) are significantly lower in RA patients (n = 134) compared to controls (n = 305; Mann-Whithney U test, $p<0.0001$)

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

**Table I.** Lower incidence of elevated IgE levels (IgE >100 IU/ml) in RA patients compared to healthy controls (two-tailed chi-square test, p = 0.001)

| Group | | IgE groups | |
|---|---|---|---|
| | | IgE low (IgE ≤ 100 IU/ml) | IgE high (IgE > 100 IU/ml) |
| RA patients | No. | 118 | 16 |
| | % | 88.1% | 11.9% |
| Controls | No. | 225 | 78 |
| | % | 74.3% | 25.7% |

**Table II.** Cortisone treatment in RA patients and IgE levels.

| Cortisone (mg)[1] | IgE (mean IU/ml) | n | P[2] |
|---|---|---|---|
| 0 | 40.2 | 22 | n.s.[3] (0.74) |
| > 0-5 | 36.5 | 54 | |
| > 5-10 | 83.0 | 37 | |
| > 10 | 45.8 | 21 | |
| Total | 51.4 | 134 | |

[1]Prednisolone equivalent in mg; [2]Kruskal-Wallis test; [3]n.s. = not significant.

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 ver-sa. 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.

**Acknowledgments**

We would like to thank all patients and controls for participating in the study. The excellent technical assistance of Ms. Uta Schellenberg is gratefully acknowledged. We are grateful to Ms. Bridget Colvin, BS for revision of the English. We also thank for the financial support: H.H. is supported by a scholarship of the Stiftung Hämotherapie Forschung, Bonn, Germany.

**References**

1. GABRIEL SE: The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am* 2001; 27: 269-81.
2. SINGAL DP, LI J, ZHU Y: Genetic basis for rheumatoid arthritis. *Arch Immunol Ther Exp (Warsz)* 1999; 47: 307-11.
3. CORNELIS F, FAURE S, MARTINEZ M *et al*.: New susceptibility locus for rheumatoid arthritis suggested by a genome-wide linkage study. *Proc Natl Acad Sci USA* 1998; 95: 10746-50.
4. OTTO JM,CS-SZABO G, GALLAGHER J *et al*.: Identification of multiple loci linked to inflammation and autoantibody production by a genome scan of a murine model of rheumatoid arthritis. *Arthritis Rheum* 1999; 42: 2524-31.
5. BARRERA P, FAURE S, PRUD'HOMME JF *et al*.: European genetic study on rheumatoid arthritis:is there a linkage of the interleukin-1 (IL-1), IL-10 or IL-4 genes to RA ? *Clin Exp Rheumatol* 2001; 19: 709-14.
6. FURUYA T, SALSTROM JL, MCCALL-VINING S *et al*.: Genetic dissection of a rat model for rheumatoid arthritis:significant gender influences on autosomal modifier loci. *Hum Mol Genet* 2000; 22: 2241-50.
7. OTTO JM,CHANDRASEKERAN R,VERMES C *et al*.: A genome scan using a novel genetic cross identifies new susceptibility loci and traits in a mouse model of rheumatoid arthritis. *J Immunology* 2000; 165: 5278-86.
8. JI H,GAUGUIER D, OHMURA K *et al*: Genetic influences on the end-stage effector phase of arthritis. *J Exp Med* 2001; 194: 321-30.
9. SVENDSEN AJ, HOLM NV, KYVIK K, PETERSEN PH, TOPIC PJ: Relative importance of genetic effects in rheumatoid arthritis:historical cohort study of Danish nation-wide twin population. *BMJ* 2001; 323: 1-4.
10. SILMANAJ: Commentary: Do genes or environment influence development of rheumatoid arthritis ? *BMJ* 2001; 323: 4-5.
11. LAFAILLE JJ: The role of helper T cell subsets in autoimmune diseases. *Cytokine Growth Factor Rev* 1998; 9: 139-51.
12. ROMAGNANI S: The Th1/Th2 paradigm. *Immunol Today* 1997; 18: 263-6.
13. VAN ROON JAG, VAN ROY JLAM, DUITS A, LAFEBER FPJG: Proinflammatory cytokine production and cartilage damage due to rheumatoid synovial T helper-1 activation is inhibited by interleukin-4. *Ann Rheum Dis* 1995; 54: 836-40.
14. KAMRADT T, BURMESTER GR: Cytokines and arthritis: Is the Th1/Th2 paradigm useful for understanding pathogenesis ? *Rheumatology* 1998; 25: 6-8.
15. SCHUERWEGH AJ, DECLERCK LS, DESCHUTTER L, BRIDTS CH, VERBRUGGEN A, STEVENS WJ: Flow cytometric detection of type 1 (IL-2, IFN-gamma) and type 2 (IL-4,IL-5) cytokines in T-helper and T-suppressor/cytotoxic cells in rheumatoid arthritis, allergic asthma and atopic dermatitis. *Cytokine* 1999; 11: 783-8.
16. HILLIQUIN P, ALLANORE Y, COSTE J, RENOUX M, KAHAN A, MENKÈS CJ: Reduced incidence and prevalence of atopy in rheumatoid arthritis. Results of a case-control study. *Rheumatology* 2000; 39: 1020-6.
17. VERHOEF CM, VAN ROON JAG, VIANEN ME, BRUIJNZEEL-KOOMEN CAFM, LAFEBER FPJG, BIJLSMA JWG: Mutual antagonism of rheumatoid arthritis and hay fever; a role for type1/type2 T cell balance. *Ann Rheum Dis* 1998; 57: 275-80.
18. RUDWALEIT M, ANDERMANN B, ALTEN R *et al*.: Atopic disorders in ankylosing spondylitis and rheumatoid arthritis. *Ann Rheum Dis* 2002; 61: 968-74.
19. KERO J, GISSLER M,HEMMINKI E,ISOLAURI E: Could TH1 and TH2 diseases coexist ? Evaluation of asthma incidence in children with coeliac disease, type 1 diabetes, or rheumatoid arthritis:A register study. *J Allergy Clin Immunol* 2001; 108: 781-3.
20. PROVENZANO G, DONATO G, BRAI G, RINALDI F: Prevalence of allergic respiratory diseases in patients with RA. *Ann Rheum Dis* 2002; 61: 281.
21. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.:American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
22. STEINBROCKER O, TRAEGER CH, BATTERMANRC: Therapeutic criteria in rheumatoid arthritis. *JAMA* 1949; 140: 659-62.
23. HACKSTEIN H, HOFMANN H, BOHNERT A, BEIN G: Definition of human interleukin-4 receptor alpha chain haplotypes and allelic association with atopy markers. *Hum Immunol* 1999; 60: 1119-27.
24. UPTON MN, MCCONNACHI A, MCSHARRY C *et al*.: Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ* 2000; 321: 88-92.
25. O'DRISCOLL BR, MILBURN HJ, KEMENY DM,COCHRANE GM, PANAYIGS: Atopy and rheumatoid arthritis. *Clin Allergy* 1985; 15: 547-53.
26. STRACHAN DP: Family size, infection and atopy: The first decade of the "hygiene hypothesis". *Thorax* 2000; 55 (Suppl. 1): S2-S10.
27. HEINRICH J, NOWAK D, WASSMER G *et al*.: Age-dependent differences in the prevalence of allergic rhinitis and atopic sensitization between an eastern and a western Germany city. *Allergy* 1998; 53: 89-93.
28. LEYNAERT B, NEUKIRCH C, JARVIS D, CHINN S, BURNEY P, NEUKIRCH F: European Community Respiratory Health Survey. Does living on a farm during childhood protect against asthma, allergic rhinitis, and atopy in adulthood ? *Am J Respir Crit Care Med* 2001; 164: 1829-34.
29. MARTINEZ FD, HOLT PG: Role of microbial burden in aetiology of allergy and asthma. *Lancet* 1999; 354 (Suppl. 2): 12-15.
30. KRAMER U, HEINRICH J, WJIST M, WICHMANN HE: Age of entry to day nursery and allergy in later childhood. *Lancet* 1999; 353: 450-4.
31. HELMS PJ: Early environmental influences in the development of asthma and atopic disease. *Monaldi Arch Chest Dis* 2001; 56:265-9.
32. DUGOWSON CE, KOEPSELL TD, VOIGT LF, BLEY L, NELSON JL, DALING JR: Rheumatoid arthritis in women. Incidence rates in group health cooperative, Seattle, Washington, 1987-1989. *Arthritis Rheum* 1991; 34: 1502-7.
33. SPECTOR TD, HART DJ, POWELL RJ: Prevalence of rheumatoid arthritis and rheumatoid factor in women: evidence for a secular decline. *Ann Rheum Dis* 1993; 52: 254-7.
34. GASTONJSH: Will the increasing prevalence of atopy have a favourable impact on rheumatoid arthritis ? *Ann Rheum Dis* 1998; 57: 265-7.