Association of anti-cyclic citrullinated peptide antibodies with subclinical atherosclerosis in patients with rheumatoid arthritis

Article *in* Annals of the rheumatic diseases · June 2008

DOI: 10.1136/ard.2007.073718 · Source: PubMed

CITATIONS
78

READS
49

6 authors, including:

Roberto Gerli
Università degli Studi di Perugia
406 PUBLICATIONS **10,080** CITATIONS
SEE PROFILE

Elena Bartoloni
Università degli Studi di Perugia
210 PUBLICATIONS **3,449** CITATIONS
SEE PROFILE

Gaetano Vaudo
Università degli Studi di Perugia
164 PUBLICATIONS **4,116** CITATIONS
SEE PROFILE

Yehuda Shoenfeld
Tel Aviv University
1,634 PUBLICATIONS **71,683** CITATIONS
SEE PROFILE

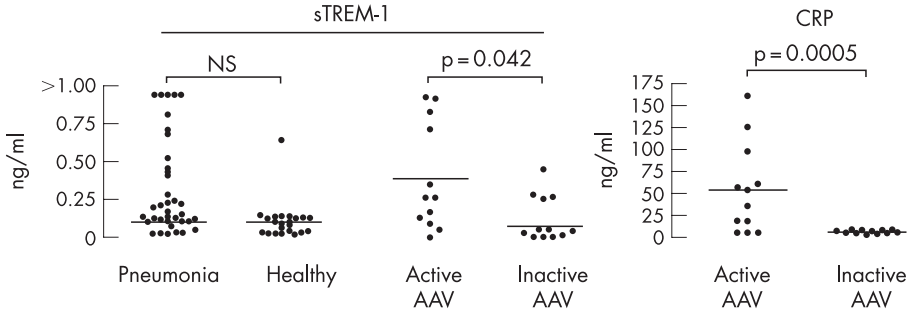

Figure 1 Serum levels of sTREM-1 in healthy blood donors, patients with pneumonia, and in patients with active versus inactive antineutrophil cytoplasmic antibody-associated vasculitis (AAV). In patients with active versus inactive AAV, C-reactive protein (CRP) levels are also shown. Each dot represents an individual measurement, bars indicate median values. Note the high levels of sTREM-1 that can be observed in active AAV.

TREM-1. To that end we assessed sTREM-1 levels in patients with active versus inactive AAV.

In a retrospective analysis we measured sTREM-1 levels in 12 patients with AAV (seven female, five male, mean age at diagnosis 65 years (range 22–77 years), Wegener granulomatosis (n = 9), Churg–Strauss angiitis (n = 2) and microscopic polyangiitis (n = 1)).[5] The Birmingham Vasculitis Activity Score (BVAS) was used to clinically grade disease activity. As a control, sTREM-1 levels were also measured in 23 healthy individuals and in 40 consecutively sampled patients with the clinical diagnosis of pneumonia.

In all patients, sTREM-1 and—as a non-specific measure of systemic inflammation—C-reactive protein (CRP) levels were quantified at the time of active disease (median BVAS 13 (range 3–20)), and during subsequent remission (median BVAS 1 (range 0–4)). Median time between sampling was 16.4 months (range: 3–61 months). In none of the patients infection was detected at the time of sampling.

The median sTREM-1 and CRP levels at the time of active AAV were 0.27 ng/ml (range 0–0.96 ng/ml) and 44 mg/l (range 4–160.5 mg/l), respectively. In samples obtained during subsequent remission, median sTREM-1 and CRP levels were 0.06 ng/ml (range 0–0.5 ng/ml) and 5.5 mg/l (range 3–8 mg/l) respectively (fig 1). In line with previously published reports, increased sTREM-1 levels (>0.25 ng/ml) were detected in 17 of 40 patients with pneumonia (42.5%), but only one of 23 healthy individuals (4.3%).[5] Median sTREM-1 levels in patients with pneumonia (range 0 to >1 ng/ml) and in healthy individuals (range 0–0.67 ng/ml) did not differ (0.11 ng/ml each) (fig 1).

Thus, in this small retrospective study, we show that elevated serum levels of sTREM-1 can be detected in patients with active AAV (high BVAS, increased CRP). Intriguingly, in AAV, sTREM-1 levels were significantly higher at times of active disease as compared with remission. As engagement of TREM-1 on neutrophils can induce phagocytosis, respiratory burst and degranulation,[2] it is tempting to speculate that autoimmune triggering of this receptor plays a pathogenic role in AAV. Further, ideally prospective studies will have to assess whether increased levels of sTREM-1 precede active AAV, and how sTREM-1 levels relate to ANCA titre dynamics.

T Daikeler,[1] S Regenass,[1] A Tyndall,[1] M M Gencay,[2] M Roth,[2] M Christ-Crain,[3] B Müller,[3] C Hess[4]

[1] Department of Rheumatology, University Hospital Basel, Switzerland; [2] Pulmonary Cell Research, Department of Research, University Hospital Basel, Switzerland; [3] Division of Endocrinology, University Hospital Basel, Switzerland; [4] Department of Internal Medicine and Immunobiology Laboratory, University Hospital Basel, Switzerland

Correspondence to: Thomas Daikeler, Department of Rheumatology, University Hospital Basel Switzerland, Petersgraben 4, CH-4031 Basel Switzerland; tdaikeler@uhbs.ch

Funding: CH is supported by a Swiss National Science Foundation (SNF) professorship grant (PP00B-114850).

Competing interests: None.

Accepted 27 July 2007

Ann Rheum Dis 2008;**67**:723–724. doi:10.1136/ard.2007.076547

REFERENCES

1. **Kamesh L,** Harper L, Savage CO. ANCA-positive vasculitis. *J Am Soc Nephrol* 2002;**13**:1953–60.
2. **Bouchon A,** Facchetti F, Weigand MA, Colonna M. TREM-1 amplifies inflammation and is a crucial mediator of septic shock. *Nature* 2001;**410**:1103–7.
3. **Gibot S,** Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. *N Engl J Med* 2004;**350**:451–8.
4. **Harper L,** Savage CO. Leukocyte-endothelial interactions in antineutrophil cytoplasmic antibody-associated systemic vasculitis. *Rheum Dis Clin North Am* 2001;**27**:887–903.
5. **Muller B,** Gencay MM, Gibot S, Stolz D, Hunziker L, Tamm M, *et al*. Circulating levels of soluble triggering receptor expressed on myeloid cells (sTREM)-1 in community-acquired pneumonia. *Crit Care Med* 2007;**35**:990–1.

Association of anti-cyclic citrullinated peptide antibodies with subclinical atherosclerosis in patients with rheumatoid arthritis

Rheumatoid arthritis (RA) is associated with increased mortality, predominantly due to accelerated atherosclerosis.[1] Traditional cardiovascular disease (CVD) risk factors cannot fully account for this increased propensity and it seems that the sustained inflammatory state of RA represents a crucial element for enhanced atherosclerotic risk.[1 2] In fact, CVD mortality in RA appears to be predicted by the level of disease activity and severity of joint damage and extra-articular manifestations.[2 3] Some immunological markers, such as rheumatoid factor or antinuclear antibodies, are more often encountered in RA with extra-articular manifestations.[4] Anti-cyclic citrullinated peptide (anti-CCP) antibodies have been shown to be highly specific for RA and are predictors of disease severity, even stronger than rheumatoid factor.[5] They have been also associated with disease extra-articular manifestations,[4] but their association with CVD morbidity has never been examined.

To evaluate the effect of anti-CCP on atherosclerotic damage in RA, carotid intima-media thickness (IMT) of 81 consecutive

Table 1 Intima-media thickness values at different carotid artery districts (mm; mean (SD)) in patients with RA subdivided according to the presence of absence of serum anti-CCP antibodies

	Normal controls n = 75	Total patients with RA n = 81	Patients with RA anti-CCP– n = 29	Patients with RA anti-CCP+ n = 52	Anti-CCP– versus anti-CCP+P
Age (mean (SD))	61 (13)	63 (10)	62 (10)	63 (11)	0.54
Sex (males %)	29.3	28.4	13.7	36.5	0.02 (ξ^2)
Disease duration (years)	–	11 (9)	10 (7)	13 (10)	0.41
Common carotid	0.81 (0.24)	0.84 (0.22)†	0.82 (0.18)	0.85 (0.24)	0.44
Carotid bifurcation	0.89 (0.24)	1.02 (0.25)†	1.05 (0.26)	1.01 (0.24)	0.52
Internal carotid	0.74 (0.23)	0.76 (0.21)†	0.70 (0.16)	0.80 (0.23)	0.03
Carotid artery*	0.86 (0.25)	0.87 (0.19)†	0.85 (0.16)	0.89 (0.20)	0.47

*Values of carotid artery are the average of common carotid, carotid bifurcation and internal carotid intima-media thickness values.
†$p<0.05$ versus normal controls.
RA, rheumatoid arthritis; anti-CCP, anti-cyclic citrullinated peptides.

patients with RA without overt CVD was analysed by ultrasound, as described.[6] Seventy-five age- and sex-matched healthy subjects with a similar distribution of risk factors (smoking, high body mass index, hypercholesterolaemia, hypertension, diabetes mellitus and CVD family history) formed the control group. Evaluation of anti-CCP was performed in all patients by an enzyme-linked immunosorbent assay (Diastat, Axis-Shield Diagnostics, Dundee, UK). The study was approved by the local ethical committee.

IMT values were higher in the patients than in controls at all artery domains examined (common, bifurcation and internal carotid) (table 1). Patients with RA with detectable circulating anti-CCP had higher IMT at internal carotid arterial wall than patients without evidence of these antibodies. The fact that we found differences only at the internal carotid may be due to a low number of enrolled patients, but it may also be explained by the observation that atherosclerosis primarily involves the upper carotid tract (internal carotid and bifurcation).[7]

The patients who were anti-CCP positive did not differ from the other patients for age, disease duration, traditional risk factors and treatment (data not shown), but included a higher number of males. This finding agrees with the demonstration that male patients with RA are more likely to be seropositive for, and have higher titres of anti-CCP compared with female patients.[8] Although this may represent a confounding factor that might explain the higher internal carotid IMT found in the patients who were anti-CCP positive, a multivariate analysis showed that only age, smoking and anti-CCP, but not sex or other traditional risk factors, were predictors of internal carotid thickening in our series.

The role of age and smoking as predictors of atherosclerosis in RA has been described in several studies.[1 2 9 10] However, to our knowledge, this is the first report showing an association between anti-CCP and subclinical atherosclerosis in patients with RA. The finding that smoking may trigger immunity to citrullinated proteins in genetically predisposed subjects with RA [10] may represent a fascinating pathogenic link between smoking, anti-CCP and atherosclerosis acceleration in RA. Further studies with higher number of patients are ongoing to verify the benefit of anti-CCP determination in identifying patients with RA at high risk for CVD.

R Gerli,[1] E Bartoloni Bocci,[1] Y Sherer,[2] G Vaudo,[3] S Moscatelli,[1] Y Shoenfeld[2]

[1] Rheumatology Unit, Department of Clinical & Experimental Medicine, University of Perugia, Italy; [2] Center for Autoimmune Diseases, Department of Medicine B, Chaim Sheba Medical Center, Tel-Hashomer, Israel; [3] Section of Internal Medicine and Angiology, Department of Clinical & Experimental Medicine, University of Perugia, Italy

Correspondence to: Professor Roberto Gerli, Rheumatology Unit, Department of Clinical & Experimental Medicine, University of Perugia, Policlinico di Monteluce, I-06122 Perugia, Italy; gerlir@unipg.it

Competing interests: None.

Accepted 12 August 2007

Ann Rheum Dis 2008;**67**:724–725. doi:10.1136/ard.2007.073718

REFERENCES

1. **Shoenfeld Y,** Gerli R, Doria A, Matsuura E, Matucci Cerinic M, Ronda N, *et al*. Accelerated atherosclerosis in autoimmune rheumatic diseases. *Circulation* 2005;**112**:3337–47.
2. **Kaplan M.** Cardiovascular disease in rheumatoid arthritis. *Curr Opin Rheumatol* 2006;**18**:289–97.
3. **Turesson C,** McClelland RL, Christianson TJH, Matteson EL. Severe extra-articular disease manifestations are associated with an increased risk of first ever cardiovascular events in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;**66**:70–75.
4. **Turesson C,** Jacobsson LTH, Sturfelt G, Matteson EL, Mathsson L, Rönnelid J. Rheumatoid factor and antibodies to cyclic citrullinated peptides are associated with severe extra-articular manifestations in rheumatoid arthritis. *Ann Rheum Dis* 2007;**66**:59–64.
5. **van Venrooij WJ,** Zendman AJW, Pruijn GJM. Autoantibodies to citrullinated antigens in (early) rheumatoid arthritis. *Autoimmun Rev* 2006;**6**:37–41.
6. **Gerli R,** Schillaci G, Giordano A, Bartoloni Bocci E, Bistoni O,Vaudo G, *et al*. CD4+CD28- T lymphocytes contribute to early atherosclerotic damage in rheumatoid arthritis patients. *Circulation* 2004;**109**:2744–8.
7. **Rubba P,** Panico S, Bond MG, Covetti G, Celentano E, Iannuzzi A, *et al*. Site-specific atherosclerotic plaques in the carotid arteries of middle-aged women from southern Italy: associations with traditional risk factors and oxidation markers. *Stroke* 2001;**32**:1953–9.
8. **Jawaheer D,** Lum RF, Gregersen PK, Criswell LA. Influence of male sex on disease phenotype in familial rheumatoid arthritis. *Arthritis Rheum* 2006;**54**:3087–94.
9. **Gerli R,** Sherer Y, Vaudo G, Schillaci G, Gilburd B, Giordano A, *et al*. Early atherosclerosis in rheumatoid arthritis: effect of smoking on thickness of the carotid artery intima media. *Ann N Y Acad Sci* 2005;**1051**:281–90.
10. **Klareskog L,** Padyukov L, Alfredsson L. Smoking as a trigger for inflammatory rheumatic diseases. *Curr Opin Rheumatol* 2007;**19**:49–54.

Association of the toll-like receptor 4 gene polymorphisms with Behçet's disease

Behçet's disease (BD) is a multisystemic inflammatory disorder characterised by recurrent ocular symptoms, oral and genital ulcers, and skin lesions.[1 2] The aetiology of BD remains unclear, but likely both genetic and environmental factors play an important part in BD development.

We performed a whole-genome association analysis of BD using 23 465 microsatellite markers and ultimately found significant association for 147 markers (unpublished data). One of the 147 markers is located within 100 kb from the toll-like receptor (TLR) 4 gene on chromosome 9. Among the TLR family members, TLR4 is the receptor most exhaustively investigated and has been shown to recognise and interact with heat shock protein (HSP) and lipopolysaccharide (LPS),[3 4] which are regarded as antigens in BD.[5–9] Therefore, we hypothesised that *TLR4* polymorphisms may be associated with the risk of BD and conducted single-nucleotide polymorphisms (SNPs) analysis of *TLR4* in BD. To our knowledge,

Association of anti-cyclic citrullinated peptide antibodies with subclinical atherosclerosis in patients with rheumatoid arthritis

R Gerli, E Bartoloni Bocci, Y Sherer, et al.

Ann Rheum Dis 2008 67: 724-725
doi: 10.1136/ard.2007.073718