experiment with synovial T cells from 11 patients with chlamydia triggered ReA (SI 20.8 (15.51)) (group 2). In this case none of the patients had a T cell proliferation to Ye 19 kDa (SI 1.72 (1.5)) (fig 1). In 15 patients with the clinical diagnosis of ReA or undifferentiated oligoarthritis synovial T cells proliferated to mitogen, but not to any of the ReA triggering bacteria or Ye 19 kDa (SI 1.78 (1.25)) (group 3, fig 1).

Because the Ye 19 kDa as the β subunit of urease[6] is a yersinia antigen not shared by other ReA triggering enterobacteria we believe that we have identified the cause of disease of a substantial number of patients with ReA in clinical practice which would not have been known by other means. We assume that Ye 19 kDa used in synovial T cell proliferation assays is a useful antigen to specify Ye as the disease triggering bacteria and might be of diagnostic value in ReA.

Authors' affiliations
H Appel, M Rudwaleit, P Wu, M Grolms, J Sieper, Benjamin Franklin Medical Centre, Division of Gastroenterology and Rheumatology, Free University Berlin, Germany
P Wu, J Sieper, Deutsches Rheumaforschungszentrum Berlin, Germany
A Mertz, Medical Centre Augsburg, Division of Nephrology, Augsburg, Germany

Correspondence to: Professor J Sieper; hjsieper@zedat.fu-berlin.de

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Leflunomide and hypertension

B Rozman, S Praprotnik, D Logar, M Tomšič, M Hojnik, M Kos-Golja, R Accetto, P Dolenc

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Leflunomide is a new isoxazole drug with disease modifying properties for the treatment of rheumatoid arthritis (RA). Hypertension has been mentioned as a common side effect of the treatment. It was found in up to 10.6% of patients receiving 25 mg leflunomide in a phase II study.[1] New onset hypertension occurred in 3.7% of patients in a phase III European study,[2] and in 2.1% of patients, with a mean increase in systolic and diastolic blood pressure of 2.2 and 1.9 mm Hg, respectively, in an American phase III study.[3] There was no evidence that hypertension was related to an impairment of renal function or proteinuria. The changes in blood pressure during leflunomide treatment have not been studied in detail.

PATIENTS AND METHODS

Thirty consecutive patients fulfilling the American Rheumatism Association criteria for RA were recruited into a prospective study and treated with standard doses of leflunomide. Other enrolment criteria included stable treatment with non-steroidal anti-inflammatory drugs up to the maximum recommended dose and/or corticosteroid treatment up to 10 mg/day for at least three months before starting treatment with leflunomide. The patients were followed up at two week intervals. A trained nurse according to the Slovenian and WHO/ISH hypertension guidelines measured blood pressure.[4] Automatic oscillometric monitors (Spacelabs 90209) were used for ambulatory blood pressure monitoring (ABPM).[5] Seventeen patients finished the study according to the protocol with 6.5 (1) months between the two ABPM procedures.

RESULTS

A statistically significant increase in conventional blood pressure measurements of both systolic and diastolic blood pressure was seen (table 1). The rise in systolic blood pressure was seen relatively early—in 2–4 weeks (from 127.03 (20.2) mm Hg to 134.1 (24.3) mm Hg, p=0.034). On the contrary, the rise in diastolic blood pressure was not significant after 2–4 and 6–8 weeks, respectively. In 7/17 patients, the initially normal blood pressure values exceeded the systolic and/or diastolic blood pressure values of 140/90 mm Hg in the follow up measurements. Moreover, in four patients the systolic blood pressure was, at least once in the follow up period, more than 40 mm Hg and diastolic blood pressure more than 20 mm Hg above the initial values. According to the ambulatory blood pressure monitoring (ABPM) measurements the overall trend after the start of leflunomide treatment was an increase in both systolic and diastolic blood pressure and heart rate, which was highly statistically significant (table 1). Figure 1 shows individual changes in blood pressure and heart frequency.

DISCUSSION

Using standardised conditions of blood pressure measuring (not the case in phase II and phase III clinical trials) and ABPM, we confirmed the blood pressure rises during treatment with leflunomide. Adding to the knowledge from previous studies, we showed that a statistically significant rise in systolic blood pressure was apparent already after

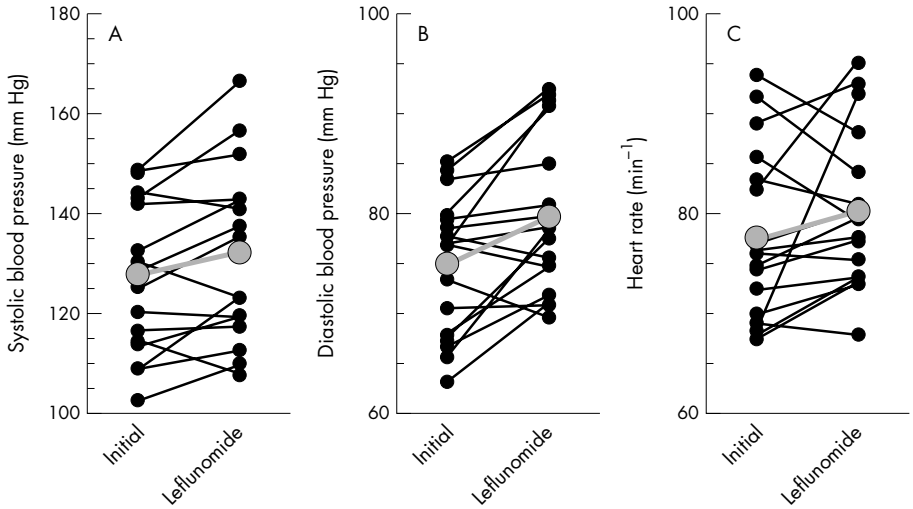

Figure 1 Changes in (A) systolic blood pressure, (B) diastolic blood pressure, and (C) heart rate in 17 patients with RA treated with leflunomide. Twenty four hour averages of individual patients during ABPM performed during and after 6.5 (1) months of treatment with leflunomide are shown. The overall trends in individual variables are shown by the grey line.

2–4 weeks of the treatment, thus pointing to the need for early blood pressure monitoring. By contrast, the rise in diastolic blood pressure appeared later. Hypertensive values in individual patients suggest that regular measuring of blood pressure is required during treatment with leflunomide.

Employing ABPM, we confirmed the significant rise in blood pressure during the leflunomide treatment, thus making the role of the "white coat" phenomenon unlikely. It should be mentioned that it has been confirmed that non-invasive ABPM has no effect on blood pressure because of discomfort during cuff inflation. We are also not aware of any special device developed to measure blood pressure in patients with painful limbs. However, as a clinically relevant (>5 joints) improvement in tender and swollen joint count was seen in 14 (83%) of the 17 patients analysed, the degree of pain imposed by blood pressure measurements and its effect on blood pressure were expected to decrease rather than rise during the study.

The results do not allow us to speculate on the mechanism of the blood pressure increase associated with the leflunomide treatment. As the heart rate also rises during leflunomide treatment, it has been assumed that hypertension may be caused by an increased sympathetic drive.

Table 1 Conventional systolic and diastolic blood pressure measurements, 24 hour averages of blood pressure, and heart frequency before (initial ABPM) and after treatment with leflunomide (final ABPM) in 17 patients with rheumatoid arthritis. Twenty four hour, day time (6 00 am to 10 00 pm), and night time (10 00 pm to 6 00 am) mean values and standard deviations are shown. Statistical significance of differences was tested with Student's *t* test. p Values of ⩽0.05 were considered significant

	Initial measurement	Final measurement	*t* Test	Significance (p)
Conventional measurements (mean)				
Systolic blood pressure (mm Hg)	127.3 (20.2)	140.7 (20.1)	3.55	0.003
Diastolic blood pressure (mm Hg)	76.7 (9.3)	84.0 (8.6)	3.08	0.007
ABPM (mean)				
Systolic blood pressure (mm Hg)	127.8 (19.7)	132.1 (21.4)	3.01	0.003
Diastolic blood pressure (mm Hg)	74.9 (12.4)	79.7 (13.0)	5.43	0.000
Mean arterial pressure (mm Hg)	93.6 (14.8)	98.7 (15.8)	4.76	0.000
Pulse pressure (mm Hg)	52.9 (14.0)	52.4 (15.5)	0.46	NS
Heart frequency (min^{-1})	77.6 (13.7)	80.2 (13.5)	2.71	0.007
Day time (6 00 am to 10 00 pm)				
Systolic blood pressure (mm Hg)	130.2 (18.2)	135.2 (19.6)	5.18	0.000
Diastolic blood pressure (mm Hg)	77.8 (11.4)	83.1 (11.7)	9.04	0.000
Mean arterial pressure (mm Hg)	96.1 (13.4)	83.1 (11.7)	7.86	0.000
Pulse pressure (mm Hg)	52.5 (14.2)	52.1 (15.4)	0.44	NS
Heart frequency (min^{-1})	81.8 (13.7)	83.7 (13.3)	2.83	0.005
Night time (10 00 pm to 6 00 am)				
Systolic blood pressure (mm Hg)	121.9 (20.6)	124.1 (20.6)	1.20	NS
Diastolic blood pressure (mm Hg)	69.1 (12.2)	72.3 (11.8)	3.07	0.002
Mean arterial pressure (mm Hg)	87.8 (15.5)	91.5 (14.6)	2.77	0.006
Pulse pressure (mm Hg)	52.8 (13.3)	51.7 (15.0)	0.86	NS
Heart frequency (min^{-1})	68.7 (9.2)	72.9 (10.9)	4.78	0.000

This hypothesis remains to be tested. The changes in the raised blood pressure after six months of leflunomide treatment will be clarified after the final report of all extended studies.

Authors' affiliations
B Rozman, S Praprotnik, D Logar, M Tomšič, M Hojnik, M Kos-Golja, Department of Rheumatology, Medical Centre Ljubljana, Vodnikova 62, 1000 Ljubljana, Slovenia
R Accetto, P Dolenc Department of Hypertension, Medical Centre Ljubljana

Correspondence to: Dr B Rozman; kc.lj.rozman@siol.net

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Adhesion molecule expression in the synovial membrane of psoriatic arthritis

V Riccieri, A Spadaro, E Taccari, A Zoppini, E Koo, J Ortutay, M Sesztak, I Markus

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Endothelium may play a part in the pathogenesis of long-standing psoriatic arthritis (PsA),[1] whereas a higher vascularisation and a less intense adhesion molecule expression have been found in PsA synovial membrane compared with rheumatoid arthritis.[2] Some proinflammatory molecules, such as tumour necrosis factors (TNFs), can induce synovial endothelial cells and fibroblast-like synoviocytes to express adhesion molecules.[3 4]

PATIENTS AND METHODS

In two groups of patients with PsA—eight patients with synovitis of <1 year and six patients with synovitis >1 year—we studied the expression and pattern of the synovial distribution of endothelial leucocyte adhesion molecule-1 (ELAM-1 or E-selectin) (CD62E), intercellular adhesion molecule-1 (ICAM-1) (CD54), vascular cell adhesion molecule-1 (VCAM-1) (CD106) (Immunotech, Marseille, France), and of TNFα and TNFβ cytokines (Chemicon International, Temecula, CA, USA) using a standard three stage immunoperoxidase labelling technique (LAB VISION, Fremont, CA, USA).[5] The lining layer, the infiltrating elements, and the endothelial cells were evaluated for the number of positive cells per high power field (×40).[6]

RESULTS

Table 1 summarises the main clinical and laboratory data of the two groups; no significant clinical or laboratory differences were seen.

E-selectin was present more often at endothelial, cellular infiltrate, and lining layer levels in 7/8 (88%) patients with a disease duration <1 year, where only 3/6 patients (50%) with disease duration >1 year were positive. ICAM-1 was

Table 1 Main clinical and demographic features of 14 patients with PsA with a disease duration of less (group 1) or more (group 2) than one year

Patient number	Sex	Age (years)	Duration of arthritis (years)	Duration of psoriasis (years)	PASI	Ritchie index	Subgroup	CRP (mg/l)	ESR (mm/1st h)	Treatment
Group 1										
1	F	60	<1	1	3.2	17	Polyarthritis	5	14	NSAIDs
2	F	28	<1	1	4.5	11	Polyarthritis	4	28	NSAIDs
3	F	48	<1	<1	0.3	3	Oligoarthritis	35	52	Steroids
4	M	37	<1	4	0.9	18	Polyarthritis	6	8	NSAIDs
5	M	31	<1	2	0.3	9	Polyarthritis	12	24	None
6	F	35	<1	1	9.0	20	Polyarthritis	24	66	NSAIDs
7	F	25	<1	19	2.1	5	Oligoarthritis	6	16	HCQ/NSAIDs
8	F	35	<1	18	0.9	15	Polyarthritis	6	23	HCQ/NSAIDs
Group 2										
1	M	35	2	10	3.1	9	Polyarthritis	21	38	NSAIDs
2	M	36	5	13	6.6	10	Polyarthritis	80	86	MTX/steroids
3	M	53	3	37	8.9	21	Polyarthritis	6	3	NSAIDs
4	M	39	3	2	1.2	9	Polyarthritis	25	11	SSZ
5	M	43	5	30	4.2	6	Oligoarthritis	6	8	NSAIDs
6	M	50	10	25	9.0	15	Polyarthritis	6	10	NSAIDs

PASI, Psoriasis Areas Severity Index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate (Westergren); NSAIDs, non-steroidal anti-inflammatory drugs; HCQ, hydroxychloroquine; MTX, methotrexate; SSZ, sulfasalazine.