CHAPTER 12

Blood pressure changes in recent onset rheumatoid arthritis patients treated with four different treatment strategies

A post hoc analysis from the BeSt trial

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ABSTRACT

Objective: To evaluate the effect of disease activity and antirheumatic treatment on blood pressure (BP) in patient with recent-onset rheumatoid arthritis (RA).

Methods: 508 patients with RA were randomised to receive (1) sequential monotherapy, (2) step-up combination therapy, (3) initial combination with prednisone or (4) with infliximab. Systolic and diastolic blood pressure (SBP, DBP), disease activity score (DAS) and body mass index (BMI) were evaluated every 3 months. A linear mixed model was used to model SBP and DBP in each treatment group during year 1, adjusting for baseline BP, changes in BMI, DAS and cardiovascular medication.

Results: In all groups, mean SBP and DBP were lower for patients with DAS ≤2.4 than for patients with DAS >2.4. In addition, patients initially treated with infliximab (group 4) had a larger decrease in SBP and DBP over time than patients in groups 1-3. The decrease in BP was also observed in patients treated with infliximab after failure on conventional disease-modifying antirheumatic drugs in groups 1-3. The decrease in BP associated with treatment with infliximab occurred irrespective of the DAS response.

Conclusion: A lower DAS is associated with lower BP. An additional BP decrease was observed in patients treated with infliximab. Further research is needed to confirm the effect of infliximab on BP.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease which is associated with a higher prevalence of cardiovascular morbidity and mortality, possibly through effects on blood vessels that resemble the pathophysiology of atherosclerosis.[1,2] Antirheumatic treatment aims at diminishing disease activity and thereby probably decreases cardiovascular risk.[3] Various antirheumatic drugs may have other favourable and/or unfavourable effects on cardiovascular risk.[4-13]

Because cardiovascular diseases account for a considerable burden of morbidity and mortality in patients with RA, the effect on cardiovascular risk should be considered when choosing a treatment strategy. Hypertension, a risk factor for developing cardiovascular disease, is highly prevalent in patients with RA.[14] We analysed the relationship between disease activity and blood pressure (BP) and the effect of four different RA treatment strategies on BP during the first two years of treatment.

PATIENTS AND METHODS

The BeSt study is a multicenter randomised clinical trial in disease-modifying antirheumatic drug (DMARD)-naïve patients with active RA (disease duration ≤2 years) comparing four different treatment strategies: sequential monotherapy (group 1, n=126), step-up combination therapy (group 2, n=121), initial combination therapy with prednisone (group 3, n=133) and initial combination therapy with methotrexate and the tumour necrosis factor α (TNFα) inhibitor infliximab (group 4, n=128). Details of the study, including data about antirheumatic treatment in the four treatment arms, have been published previously.[15,16]

Treatment was adjusted based on 3-monthly disease activity score measurements (DAS44).[17] If a patient had a DAS >2.4, treatment was adjusted according to the pre-defined protocol for each group. If the DAS was ≤2.4 (low disease activity (LDA)) for at least 6 months, medication was tapered to a maintenance dose. Every 3 months, as part of a vital signs check, single measurements of systolic and diastolic blood pressure (SBP and DBP, respectively) were performed by trained nurses, blind to the treatment allocation. BP was measured according to local clinical standards: in 16 centers a sphygmomanometer plus stethoscope was used and in four centers electronic devices were used. For each patient, the measurement method was the same during the study period. BP readings were performed at least one hour before or 4 weeks after, administration of infliximab (infliximab infusions every 8 weeks). Patients were classified into four DAS categories at each 3-monthly visit: remission (DAS <1.6), LDA (DAS ≥1.6 but ≤2.4), moderate disease activity (MDA, DAS >2.4 but ≤3.7) and high disease activity (HDA, DAS >3.7). Patients with a DAS <1.6 from 6 to 24 months (one DAS ≥1.6 allowed) were classified as 'continuous remission'. Patients with a DAS >2.4 from 6 to 24 months, (one DAS £2.4 allowed) were classified as 'continuous clinical failure'.

Statistical analysis

The SPSS 16.0 software package was used. Baseline characteristics were analysed using one-way analysis of variance, the Kruskal-Wallis test and the chi-square test. Two different linear mixed model (LMM) analyses were performed for SBP and DBP, all with the unstructured covariance matrix. The first LMM was performed to compare SBP and DBP among the different DAS-categories based on all nine BP measurements per patient, corrected for age, gender, body mass index (BMI), the use of antihypertensive medication at baseline and the use of non-steroidal anti-inflammatory drugs (NSAIDs)/ cyclo-oxygenase-2 inhibitors (COXIBs) at baseline and during follow-up. Then LMM was used to model SBP and DBP during the first year of follow-up because from the protocol it follows that patients who were initially treated with infliximab or prednisone used it for at least 7.5 to 9 months. SBP and DBP at the four follow-up visits of year 1 were used as outcomes, with time (as factor) and baseline SBP or DBP, randomisation, age, gender, NSAID/COXIB use at baseline and during each follow-up visit, antihypertensive drug use at baseline, delta DAS and delta BMI (both for each visit compared with baseline) as fixed effects and a random patient effect.

RESULTS

The baseline characteristics between the four treatment groups were comparable.[15] Mean (SD) BP (mmHg) at baseline was high to normal in all groups: 138 (20) /84 (10), 140 (21) /85 (12), 136 (21) /85 (12) and 136 (20) /84 (11) for groups 1-4 respectively. At baseline, mean (SD) DAS was 4.4 (0.9), 34% smoked and mean (SD) BMI was 26 (5) kg/m^2. Of all patients, 22% had a medical history of cardiovascular disease, comprising mainly hypertension (31%), peripheral vascular disease (26%) and acute coronary syndrome (19%). In groups 1-4, 14%, 17%, 14% and 7% of patients were on anti-hypertensive medication at baseline, whereas 87%, 80%, 89% and 87% used NSAIDs or COXIBs. Detailed baseline characteristics and cardiovascular comedication at baseline are shown in *table 1*. During the 2 years of the study, 27 patients were lost to follow-up.

Mean DAS improved earlier in patients in treatment group 3-4 than in group 1-2. From year 1 onwards, disease activity was comparable and stable in all groups.[16] Patients with LDA (DAS ≤2.4) had, on average, lower SBP and DBP than patients with MDA/HDA (DAS >2.4) (LMM, *figure 1*) also after correction for age, gender, BMI and the use of antihypertensive medication and NSAIDs/COXIBs at baseline and during follow-up. A similar effect was observed for the mean DBP values.

Figure 2 shows the progression of SBP and DBP in the four treatment groups over time. After correction for the change in DAS from baseline, baseline SBP, age, gender, NSAID/ COXIB at baseline and during follow-up, antihypertensive drug use at baseline and delta BMI, longitudinal data analysis of the first year (LMM) showed that initial combination treatment with infliximab was associated with a reduction in SBP of 4.8 mmHg compared to sequential monotherapy (p=0.001), 3.0 mmHg compared to step-up combination therapy (p=0.04) and 4.5 mmHg compared to initial combination treatment with prednisone (p=0.002). Patients in group 4 also had lower DBP than patients in the other groups, although this was less pronounced and partly non-significant *(table 2)*. No statistically significant differences were found between the other treatment groups, with the exception of a decrease in DBP of 2.0 in group 3 compared to group 1 (*table 2*). Study center and the use of leflunomide or ciclosporin did not influence the association between treatment and BP and were therefore omitted from the analysis.

In group 4, 22 patients (17%) were classified as 'continuous clinical remission' and 11 (9%) as 'continuous clinical failure' on infliximab. A comparable decrease in BP was observed

Table 1: Baseline characteristics

	Sequential monotherapy	Step up combination therapy	Initial combination with prednisone	Initial combination with infliximab
	n=126	n=121	n=133	n=128
Age, years	54 (13)	54 (13)	55 (14)	54 (14)
Women, n (%)	86 (68)	86 (71)	86 (65)	85 (66)
DAS score	4.5 (0.9)	4.5 (0.8)	4.4 (0.9)	4.3 (0.9)
HAQ score 0-3	1.4 (0.7)	1.4 (0.6)	1.4 (0.7)	1.4 (0.7)
SHS 0-448, mean (SD)	7.3 (9.5)	6.3 (6.9)	5.9 (6.5)	7.0 (10.0)
SHS 0-448, median (IQR)	3.5 (1.5-9.5)	5.0 (1.5-8.1)	3.5 (1.5-8.5)	4.0 (1.5-8.5)
Systolic blood pressure, mmHg	137.6 (19.8)	139.8 (20.8)	136.1 (21.4)	135.7 (19.8)
Diastolic blood pressure, mmHg	84.1 (10.3)	84.6 (11.8)	84.7 (11.8)	83.6 (11.1)
Smoking yes, n (%)	45 (36)	44 (38)	44 (34)	40 (32)
BMI	26 (5)	26 (4)	26 (4)	26 (4)
Glucose	5.5 (1.3)	5.6 (1.4)	5.7 (1.5)	5.6 (1.4)
Creatinine	77 (15)	76 (14)	75 (18)	77 (13)
Cardiovascular history yes, n (%)	30 (24)	32 (26)	26 (20)	24 (19)
Hypertension	10 (8)	14 (12)	10 (8)	9 (7)
Peripheral vascular disease	9 (7)	9 (7)	4 (3)	10 (8)
Coronary heart disease	5 (4)	4 (3)	9 (7)	6 (5)
Other	10 (8)	12 (10)	5 (4)	4 (3)
History of renal disease, n (%)	0 (0)	0 (0)	1 (1)	0 (0)
Cardiovascular medication yes, n (%)	22 (18)	28 (23)	26 (20)	14 (11)
Diuretics	6 (5)	7 (6)	7 (5)	3 (2)
Betablockers	8 (6)	7 (6)	12 (9)	2 (2)
ACE / AT-2 inhibitors	6 (5)	13 (11)	4 (3)	4 (3)
Calcium channel blockers	3 (2)	3 (3)	6 (5)	3 (2)
Statines	6 (5)	6 (5)	9 (7)	5 (4)
Other	5 (4)	9 (7)	6 (5)	2 (2)
NSAID or COXIB use yes, n (%)	110 (87)	97 (80)	118 (89)	111 (87)

Data are presented as mean (standard deviation [SD]) unless otherwise noted.
ACE, angiotensin converting enzyme; AT-2, angiotensin-2 receptor; BMI, body mass index; COXIB, COX-2 inhibitors; DAS, disease activity score; HAQ, health assessment questionnaire; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drugs; SHS, Sharp-van der Heijde score

TABLE 2 Linear mixed model results with systolic and diastolic blood pressure from 3, 6, 9, and 12 months as outcome, corrected for baseline SBP, time (as factor), age, gender, use of NSAIDS/COXIBs at baseline, use of NSAIDs/COXIBs during follow-up, use of antihypertensive drugs at baseline, delta DAS, delta BMI, and a random patient effect.

	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)	
	Beta	95% CI	Beta	95% CI
Group 1 – 2	1.82	-1.11 – 4.75	1.28	-0.43 – 2.99
Group 1 – 3	0.32	-2.57 – 3.21	2.04	0.35 – 3.73
Group 1 – 4	4.83	1.98 – 7.68	2.81	1.15 – 4.48
Group 2 – 3	-1.51	-4.47 – 1.46	0.76	-0.97 – 2.49
Group 2 – 4	3.01	0.08 – 5.93	1.54	-0.17 – 3.24
Group 3 – 4	4.51	1.67 – 7.36	0.77	-0.89 – 2.44

Beta represents differences in blood pressure between the groups; > 0: first treatment group mentioned has higher blood pressure; < 0: first treatment group mentioned has lower blood pressure.

in these patients (SBP -6.8 mmHg, DBP -1.7 mmHg for patients classified as 'continuous clinical remission' and SBP-4.9 mmHg, DBP -1.0 mmHg for those classified as 'continuous clinical failure'). In accordance with the protocol, patients who had a continuous good response on infliximab and those who failed on the highest dose discontinued infliximab. At the end of the 2-year observation period when the average blood pressure appeared to return to the original value, only 18% of patients were still receiving infliximab.

In total, 70 patients in groups 1-3 switched to treatment with methotreaxaat and infliximab because of DAS >2.4 on prior treatment steps. In these 'delayed infliximab patients', SBP decreased on average 2.2 and 4.7 mmHg after 6 and 12 months, and DBP decreased 1.3 and 3.9 mmHg after 6 and 12 months. These changes are not statistically different from the changes observed in patients initially treated with methotrexate and infliximab.

DISCUSSION

This study shows that, in patients with RA, lower disease activity is associated with lower BP. This may represent part of the mechanism by which antirheumatic treatment can reduce the increased cardiovascular morbidity and mortality in RA. It is thought that systemic inflammation in RA leads to vasoconstriction and hypertension through up-regulation of the angiotensin II type 1 receptor and of endothelin and downregulation of NO_2.[14] Effective suppression of inflammation may inhibit this process, and, as a consequence, may lower BP.

Intriguingly, we found an additional reduction in SBP (up to almost 5 mmHg) and to a lesser extent (up to almost 3 mmHg) in DBP in patients treated with infliximab. Given that patients with RA are at increased risk for developing cardiovascular disease, such decreases in BP could be beneficial.[1;14;18] In the LMM, initial treatment with infliximab was associated with a reduction in SBP compared with the other strategies and also

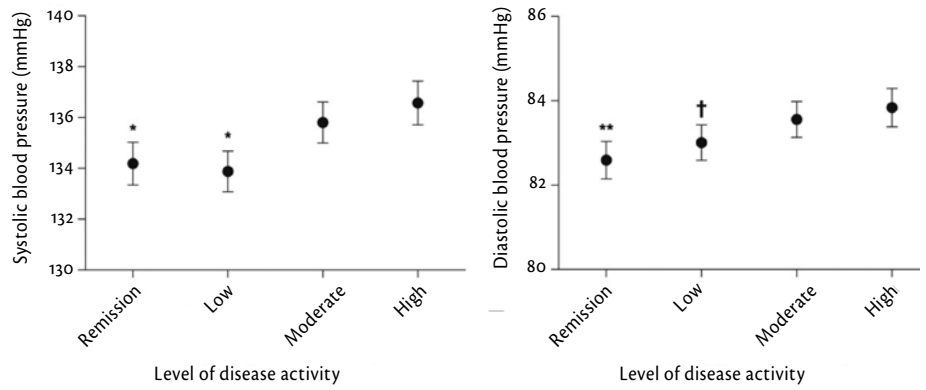

FIGURE 1 Mean values of systolic and diastolic blood pressure in relation to various levels of disease activity in patients with recent-onset rheumatoid arthritis (linear mixed model results (LMM)). At all 9 visits, patients were classified according to their disease activity level. In the LMM the relationship between the level of disease activity and systolic and diastolic blood pressure was analysed, using all 9 visits.
Remission: DAS <1.6; Low: DAS ≥ 1.6 but ≤ 2.4; Moderate: DAS >2.4 but ≤ 3.7; High: DAS >3.7. DAS, disease activity score. Error bars represent standard errors; *p < 0.01: Remission and Low versus Moderate and High; **p<0.01 Remission versus Moderate and High; #p=0.03: Low versus High

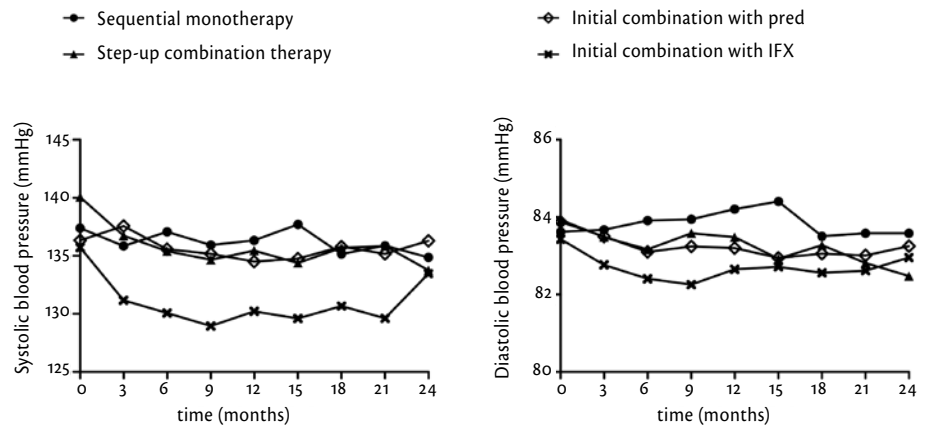

FIGURE 2 Systolic and diastolic blood pressure in the four different treatment groups during 2 years of follow-up with LMM results to account for missing values, with time (as factor), randomisation and time*randomisation as predictors

after correction for the improvement in disease activity. Decreases in SBP and DBP were observed in patients who received infliximab as initial therapy and in those who received infliximab after failing on previous treatments, although the latter had a less pronounced reduction in disease activity. Lower BP was seen in patients who failed on infliximab as well as in those who responded with continuous remission. These results

suggest that treatment with infliximab has a drug-specific effect on BP which is independent of the level of inflammation measured by the DAS. After 2 years the benefit of infliximab on SBP seems to disappear, probably due to discontinuation of infliximab in the most patients in accordance with the protocol.

To our knowledge, the effect of TNFa inhibitors on BP has not yet been described. There are, however, observations that anti-TNFa treatment is able to reverse endothelial dysfunction,[13] decrease arterial stiffness[19] and decrease plasminogen activator inhibitor-1 in patients with RA.[20]

The BeSt study was not designed to analyse BP changes associated with antirheumatic treatment. The single BP measurements, done without a standardised measurement protocol, may have led to inconsistent BP measurements. Although the possibility of bias cannot be excluded, we think it is unlikely since the data collection occurred before the hypothesis was formulated, the nurses who measured BP were blind for treatment allocation and we found that adding the variable study center to the analyses did not change the results. The use of cardiovascular concomitant medication and of NSAIDs and COXIBs could have interfered with the observed differences between the groups, although we tried to correct for this in the analyses. Ideally, our BP data should be combined with observations on the occurrence of cardiovascular adverse events. However, the BeSt study was not designed or powered to detect possible differences in such events and few have occurred within the first 2 years of the trial.

Being aware of these limitations, the decrease in BP in patients treated with methotrexate and infliximab remains an interesting and probably clinically relevant observation that needs further investigation.

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