

## SCIENTIFIC LETTER

# Irbesartan significantly reduces C reactive protein concentrations after 1 month of treatment in unstable angina

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The renin–angiotensin system (RAS) has been demonstrated to play not only an important role in cardiovascular homeostasis by influencing vascular tone and fluid–electrolyte balance, but is also involved in the atherothrombotic process, cardiac remodelling, and apoptosis.

Agents that inhibit the RAS, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs), exert considerable benefits in hypertension and heart failure. However, ACE inhibitors may not provide total inhibition of angiotensin II (Ag II) generation, because of non-ACE dependent Ag II producing mechanisms. ARBs are able to exert more specific and complete blockade of the RAS, overcoming some of the ACE inhibitor limitations. In fact they block Ag II effects on catecholamine production, vasoconstriction, aldosterone secretion, low density lipoprotein transport, hypertrophy, and cell growth, without affecting the Ag II mediated positive effects on the type II receptor, such as vasodilatation and inhibition of cell growth.<sup>1</sup>

A growing body of data has consistently described an anti-inflammatory action of ARBs. In patients with early atherosclerosis, irbesartan decreases markers of inflammation.<sup>2</sup> It has also been described that Ag II blockade improves the anti-inflammatory response of aspirin and statins in stable coronary heart disease patients.<sup>3,4</sup> However, a potential anti-inflammatory role of ARBs has not been evaluated in acute coronary syndromes (ACS), a condition in which inflammation is an acknowledged pathophysiological mechanism. In ACS both cellular and biochemical markers of inflammation have been found to be elevated. In particular C reactive protein (CRP) and interleukin-6 (IL-6) have been described in a number of studies as markers of disease activity and of future events. Therefore, we evaluated whether irbesartan, a selective Ag II blocking agent, may modulate the inflammatory response in unstable angina, by reducing CRP and the in vitro generation of IL-6 after lipopolysaccharide (LPS) challenge in unstable angina patients.

## METHODS

We studied 25 unstable angina patients (Braunwald's class IIIB), from a total of 200 patients admitted between January and November 2002 to the critical care unit or sub-intensive care unit with a diagnosis of unstable angina. Inclusion criteria were: angina at rest with at least two ischaemic episodes or one episode lasting more than 20 minutes in the preceding 24 hours, with diagnostic ST segment shift; no evidence of myocardial infarction, defined as no increase in total creatine kinase concentrations of more than twofold the reference value; no development of new Q waves. Exclusion criteria were: previous ACE inhibitor or ARB treatment, or medical indication for this therapy; ejection fraction < 40%; diabetes mellitus; hypertension; ECG abnormalities that could affect the recognition of ST segment shift; recent or chronic infective or inflammatory diseases; neoplastic disease; myocardial infarction; surgery or trauma in the previous

month. According to a 1:1 randomised, open label, protocol, subjects received irbesartan 300 mg/day (group 1) or placebo (group 2) on top of standardised conventional anti-ischaemic treatment (including in all patients at least aspirin, clopidogrel,  $\beta$  blockade, statins, and low molecular weight heparin in the first three days of hospitalisation) for one month. Group 1 included 13 patients, 10 men and three women, aged between 51–72 years old (mean (SD) 61.1 (10) years). Group 2 included 12 patients, eight men and four women, aged between 36–76 years old (mean 64.8 (12) years,  $p$  = not significant).

All patients were monitored in the critical care unit or sub-intensive care unit and underwent coronary angiography. Venous blood samples were taken from all patients at entry and one month after admission for the assessment of serum concentrations of CRP and IL-6. Coded plasma samples were stored at  $-70^{\circ}\text{C}$  and analysed for CRP and IL-6 in a single batch at the end of the study. The study was approved by the ethical committee of our institution and the patients gave their consent to the study. High sensitivity CRP was assayed in a latex enhanced immunonephelometric high sensitivity assay (Dade-Boehringer, Marburg, Germany), as previously described.<sup>5</sup>

IL-6 was measured by an enzyme linked immunosorbent assay (ELISA) (R&D USA). IL-6 was assessed before and after stimulation with 1 ng/ml LPS (*Escherichia coli* 011:B4; Sigma Chemical Co), as previously described.<sup>5</sup>

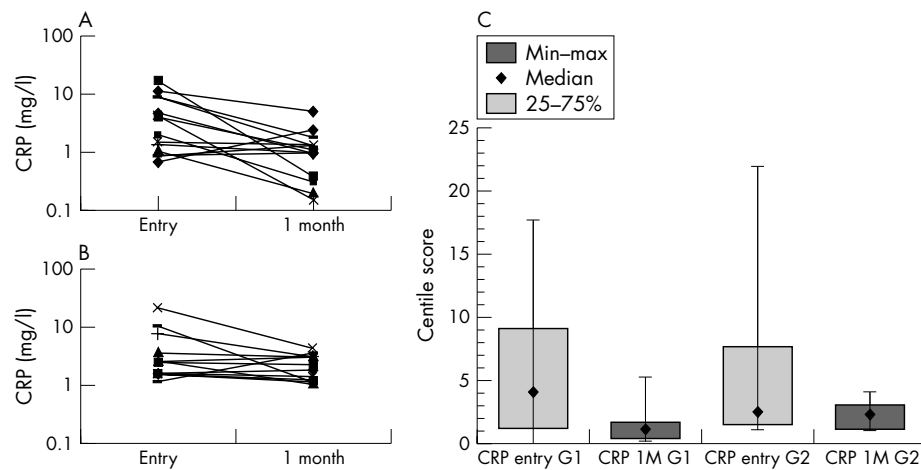
As the data were not normally distributed, non-parametric tests were used. The Mann-Whitney U test was used for comparison of CRP and IL-6 between groups and the Wilcoxon signed rank test was used for comparisons within groups. Proportions were compared with the use of the  $\chi^2$  test. CRP and IL-6 values are expressed as median and range. Values of  $p < 0.05$  (two tailed) were considered significant.

## RESULTS

At entry no significant differences in the demographic and clinical findings (age, sex, smoking habits, hypercholesterolaemia, family history of ischaemic heart disease, previous infarction, number of coronary artery disease), or in markers of inflammation were detected. In group 1 median CRP concentrations decreased after one month from 3.1 mg/l (range 0.7–17.7 mg/l) to 1.2 mg/l (range 0.16–10.07 mg/l;  $p = 0.038$ ). In group 2 no significant reductions in serum CRP concentrations were observed throughout the study; median CRP concentrations were 2.5 mg/l (range 1.1–21.9 mg/l) at entry, and 2.25 mg/l (range 0.99–4.09 mg/l) after one month, ( $p$  = not significant) (fig 1, table 1).

IL-6 in vitro generation after LPS challenge decreased in group 1 from 632 pg/ml (range 115–8635 pg/ml) to 28 pg/ml

**Abbreviations:** ACS, acute coronary syndromes; Ag II, angiotensin II; ARB, angiotensin II type 1 receptor blocker; ACE, angiotensin converting enzyme; CRP, C reactive protein; IL-6, interleukin-6; LPS, lipopolysaccharide; RAS, renin–angiotensin system



**Figure 1** CRP concentrations at entry and after one month of treatment with irbesartan in (A) group 1 and (B) group 2; (C) differences in CRP concentrations in both groups before and after treatment, expressed as median, 25–75% of the distribution and range.

**Table 1** Plasma concentrations of CRP in group 1 and group 2 at entry and after one month follow up

Group 1		Group 2	
CRP at entry (mg/l)	CRP after 1 month (mg/l)	CRP at entry (mg/l)	CRP after 1 month (mg/l)
11.36	5.2	1.57	1.82
2.02	0.32	2.48	2.99
1.08	0.2	2.51	0.99
17.7	0.4	2.31	2.25
4.28	0.16	21.97	4.09
4.79	0.94	1.48	1.12
1.39	0.99	7.6	3.02
0.89	1.29	1.1	3.5
8.93	1.83	10.31	1.07
0.7	2.44	2.5	2.25
9.21	1.29	1.5	1.2
3.99	1.11	3.5	2.9
1.57	1.38		

Group 1 includes patients treated with irbesartan; group 2 includes patients treated with placebo on top of standard anti-ischaemic therapy.

(range 13–949 pg/ml;  $p = 0.0029$ ). A trend towards reduction of IL-6 in vitro generation was found in group 2, from 4289 pg/ml (range 1887–8392 pg/ml), to 311 pg/ml (range 199–4740 pg/ml;  $p = 0.07$ ).

## DISCUSSION

Our findings show that Ag II receptor blockade with irbesartan significantly reduces plasma concentrations of CRP in unstable angina patients and might also reduce IL-6 in vitro generation after LPS challenge, a sign of inflammatory hyperreactivity and of increased vulnerability to recurrent ischaemia.<sup>5</sup> This reduction is particularly notable because it goes beyond the expected reduction in CRP from an ischaemic event and was obtained in addition to conventional treatment, including aspirin, statins, and clopidogrel,

in a relatively short time (one month) and confirms previous data on stable patients.<sup>3,4</sup>

Our data suggest that Ag II inhibition may also be a useful therapeutic tool in unstable angina without current indication for such treatment; however, whether the reduction of inflammatory markers by irbesartan, as shown in our study, is only a biochemical effect of the drug or is related to a decrease in cardiovascular events, remains to be elucidated in a larger, properly designed study.

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