Response to anti-tumour necrosis factor alpha blockade is associated with reduction of carotid intima-media thickness in patients with active rheumatoid arthritis

F. Del Porto, B. Laganà, S. Lai¹, I. Nofroni², F. Tinti¹, M. Vitale¹, E. Podestà, A. P. Mitterhofer¹;* and R. D’Amelio*²

Objectives. To determine whether tumour necrosis factor (TNF-α) blockers may reduce carotid intima-media thickness (cIMT) in patients with active rheumatoid arthritis (RA) steadily responsive to such therapy.

Methods. From 287 consecutive RA patients attending our out-patient clinic and diagnosed on the basis of the American College of Rheumatology (ACR) criteria, 49 without traditional cardiovascular risk factors and meeting the requirements for TNF-α blockers therapy were selected. Among them, 39 actually started TNF-α blockers, but only 30, who reached at least a response on the ACR 20% improvement criteria at 14 weeks, maintained during the whole year of treatment, were finally considered (group A). The remaining 10/49, homogeneous for age, sex, traditional cardiovascular risk factors, socioeconomic status, disease activity and duration, who did not consent to TNF-α-blocker administration, were used as controls (group B). Disease activity score in 44 joints (DAS44), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were evaluated before starting the study, and 3, 6, 12 months thereafter; cIMT was measured by ultrason before and 12 months thereafter only.

Results. Patients in group A showed a very significant cIMT reduction (P < 0.0001 and P < 0.0001, on the right and left side, respectively), preceded by an early and lasting significant decrease in DAS44, ESR and CRP. Moreover, a significant correlation was found between cIMT and DAS44 (r = 0.435, P < 0.05).

Conclusions. These results demonstrate that TNF-α blockade is associated with cIMT reduction in RA patients steadily responsive to therapy, probably by lowering inflammation.

Key words: Rheumatoid arthritis, Cytokines, Cardiovascular diseases, Atherosclerosis, Drug therapy, TNF-α blockers.

Introduction

The inflammatory pathways underlying atherosclerosis (ATS) have been elucidated over the last few years [1]. Impaired endothelial function is considered a key event in the early phases of the ATS process. Endothelium injury and activation lead to altered vessel permeability, increased leukocyte adhesion, chemokine and cytokine release, thus inducing and maintaining chronic inflammation, which results in plaque formation [2]. Endothelial dysfunction and inflammation are early findings in patients with rheumatoid arthritis (RA), and represent the predisposing substrate accelerating ATS [3, 4]. In these patients, in fact, increased values of common carotid artery intima-media thickness (cIMT), an ultrasonographic marker of subclinical ATS, have been observed [5, 6], primarily related to the disease duration and inflammation [7, 8]. Also in RA patients without clinically evident cardiovascular disease, the presence of carotid plaques has been positively correlated with the duration of the disease [9]. Among pro-inflammatory cytokines, tumour necrosis factor (TNF-α) plays a key role in the inflammatory process underlying both synovial and endothelial damage in RA; it has, consequently, been considered a reasonable target for effective therapy [10]. TNF-α blockers, indeed, have been found to reduce disease activity and inflammation and to improve endothelial function and lipoprotein pattern [11–14]. Recently, progression of subclinical ATS has been described in eight RA patients who had maintained a high disease activity despite at least a 2-yr treatment (median 3 yrs) with a TNF-α blocker [15], thus strengthening the hypothesis of a strong relationship between accelerated ATS and inflammation in RA.

We attempted therefore to determine whether the anti-inflammatory effect of TNF-α blockers could improve early ATS changes observed at carotid level in 30 active RA patients steadily responsive to such therapy.

Patients and methods

Patients

From March 2003 to March 2005, among 287 consecutive RA patients attending our out-patient clinic and diagnosed on the basis of the American College of Rheumatology (ACR) criteria [16], 49 were selected on the basis of the following inclusion criteria: (i) active disease [disease activity score in 44 joints (DAS44) > 3.7] despite the treatment with two disease-modifying anti-rheumatic drugs (DMARDs) for at least 3 months; (ii) no history of cardiovascular disease nor renal insufficiency, smoking habits, uncontrolled arterial hypertension (>150/90 mmHg), diabetes mellitus and hyperhomocysteinaemia (homocysteine > 15 μmol/l) despite appropriate treatment.

Thirty-nine actually started TNF-α blockers, but only 30, who achieved at least a response on the ACR 20% improvement criteria (ACR 20) at 3 months, maintained during the whole year of treatment, were actually considered (group A). The nine non-responder patients, after a variable period ranging from 3 to 8 months, underwent change in therapy, or dosage increase or...
interval administration reduction, thus being unable to meet all the inclusion criteria. However, after 12 months from enrolment they underwent carotid ultrasound evaluation.

The remaining 10 out of the 49 originally selected, homogeneous for age, sex, traditional cardiovascular risk factors, socioeconomic status, disease activity and disease duration, who did not consent to TNF-α-blocker administration, were used as controls (group B).

The option of anti-TNF-α treatment was presented to each patient by the same physician who used the same set of data explaining benefits and side effects potentially related to treatment. Fear of the toxicity and poor compliance to the proposed administration schedule were the main reasons inducing group B patients to refuse biological treatment.

All group A and B patients were receiving methotrexate (MTX: 15 mg weekly) and folic acid, as well as low (7.5 mg/day) prednisolone doses, whereas only two patients in group A and one in group B were also treated with ciclosporin A (3 mg/kg/day).

At the end of the follow-up, all group A patients were receiving the same TNF-α blocker at standard dosages: 14 infliximab (Schering-Plough S.p.A.) 3 mg/kg every 8 weeks after the induction period, and 16 etanercept (Wyeth Lederle S.p.A.) 25 mg s.c. twice weekly.

The therapeutic strategy was decided independently of the study, in accordance with the standards currently applied in Italy. This study has been ethically approved by the Faculty of Medicine Committee.

All the patients gave their written informed consent before being included in the study, which was performed according to the principles reported in the Declaration of Helsinki.

Study design
This was a prospective, observational and non-interventional study. The clinical and laboratory parameters, in all the patients, were evaluated at 0, 3, 6 and 12 months. Carotid ultrasound was performed at 0 and 12 months only.

Clinical measurement and laboratory tests
DAS44 was measured according to the ACR guidelines by using the Ritchie's index, the number of swollen joints, the erythrocyte sedimentation rate (ESR) and the general health conditions. Active disease was considered for DAS44 ≥ 3.7, and remission for DAS44 < 1.6 [17].

Response to treatment was assessed at 3, 6 and 12 months using the ACR improvement criteria, according to which patients who did not achieve at least an ACR 20 [20% of improvement from baseline values in the swollen joint count, tender joint count as well as in three out of the remaining disease activity measures: physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, patient's assessment of the physical function and either the C-reactive protein (CRP) or ESR levels] at any time, were considered non-responders [17].

At the above-reported intervals, ESR and CRP were also evaluated.

Common carotid artery evaluation
At 0 and 12 months, right (R) and left (L) carotid ultrasound was blindly performed by an experienced sonographer [18] who was unaware of the characteristics of the subjects under examination. IMT was measured in the right and left common carotid arteries, carotid bulb and the proximal portion of the internal carotid arteries using a high-resolution, B-mode ultrasound machine (Toshiba Aplio xV, Toshiba American Medical Systems, Inc., Tustin, CA, USA) with an electric linear transducer (10 MHz mid frequency, and 3 MHz colour system frequency) with a 0.01 mm resolution, following a standardized vascular protocol [5, 6, 19–21]. Participants were studied in the supine position with slight hyperextension of the neck. Three different longitudinal views (anterior oblique, lateral and posterior oblique) and a transverse view were obtained. IMT was measured at three points on the far walls of both the left and the right distal common carotid arteries, carotid bulb and the proximal portion of the internal carotid arteries. These three points were the site of greatest thickness and a point 1 cm upstream and a point 1 cm downstream from the site of greatest thickness. Values from the three locations were then averaged to produce a mean IMT for each side. After freezing the image, the digitized ultrasound images, manually captured at end-diastole were analysed and the measurement was made with electronic callipers. Power output, focus, depth of measurement and gain were standardized by using the preset program incorporated within the software package of the ultrasound equipment. The greatest distance between the lumen-intima interface and the media-adventitia interface in areas without ATS plaques was determined and was considered normal when between 0.55 and 1 mm [22]. To assess the technique reliability of the IMT measurement, the sonographer and another one blindly re-evaluated 20 subjects within a month from the first examination. The intra-reader correlation coefficient for IMT was 0.98, whereas the inter-reader was 0.93.

Statistical analysis
The results were expressed as median and mean ± S.D. Non-parametric tests have been used to perform the statistical analysis. Within each group, the results were prospectively analysed (months 3, 6, 12 vs 0) using Wilcoxon's signed-ranks test. The mean and median delta values obtained in each group were compared using the non-parametric Mann–Whitney test. The association between categorical variables was evaluated using Fisher's exact test. Spearman's non-parametric correlation was used to establish any relationship between the variables. P-value < 0.05 was considered significant.

Results
Demographic and baseline characteristics of patients and controls are shown in Table 1, whereas the results of the prospective analysis of mean values recorded at months 3, 6, 12 vs 0 in group A and B patients are shown in Table 2. Finally, comparison between group A and B patients is reported in Table 3.

Group A
Since no differences were found between patients treated with infliximab or etanercept (data not shown), the results were taken as a whole. A significant reduction of R-cIMT (P < 0.0001) and L-cIMT (P < 0.0001) (from 0.74 ± 0.13 to 0.62 ± 0.14 mm and from 0.76 ± 0.15 to 0.63 ± 0.13 mm, respectively) was observed after 1 yr of therapy. After 3 months of anti-TNF-α therapy, significant reductions in comparison with baseline of DAS44 (P < 0.0001), ESR (P < 0.0001) and CRP (P < 0.0001) were evident (Table 2). Finally, a significant correlation was observed between DAS44 and cIMT (r = 0.435, P < 0.05).

At the end of the follow-up, cIMT values were reduced in 26 patients and unchanged in four. At the same time, mean DAS44 value decreased from 5.64 ± 1.09 to 3.34 ± 0.77, mean ESR value from 31.67 ± 18.88 to 18.40 ± 10.64 mm/h and mean CRP value from 14.79 ± 13.90 to 4.22 ± 3.93 mg/l. In 26 patients, a DAS44 < 3.7 was obtained. Three out of the four patients who did not achieve any improvement in cIMT maintained a DAS44 > 3.7.

No significant differences were found in other evaluated parameters (data not shown).
Common cIMT values in the nine non-responder patients excluded from the study, showed a stable or a worsening trend (data not shown).

**Group B**

No significant differences were found in the mean values of the investigated parameters, although some reductions were observed in the DAS₄₄, CRP and ESR values (Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A Mean ± S.D.</th>
<th>Group B Mean ± S.D.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55.28 ± 9.20</td>
<td>55.14 ± 11.99</td>
<td>0.37</td>
</tr>
<tr>
<td>Sex</td>
<td>25 F (83%)</td>
<td>8 F (80%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>6.60 ± 5.12</td>
<td>6.90 ± 2.47</td>
<td>0.57</td>
</tr>
<tr>
<td>RF</td>
<td>17.00 ± 10%</td>
<td>6.00 ± 60%</td>
<td>0.85</td>
</tr>
<tr>
<td>DAS₄₄ (mg/dl)</td>
<td>5.64 ± 1.09</td>
<td>5.24 ± 1.18</td>
<td>0.30</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>14.79 ± 13.90</td>
<td>14.76 ± 9.12</td>
<td>0.44</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>31.67 ± 18.88</td>
<td>30.40 ± 12.55</td>
<td>0.76</td>
</tr>
<tr>
<td>BMI</td>
<td>25.6 ± 3.46</td>
<td>25.67 ± 4.24</td>
<td>0.75</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>10.86 ± 3.11</td>
<td>11.83 ± 2.57</td>
<td>0.58</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>79 ± 8</td>
<td>77.22 ± 7</td>
<td>0.64</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>79 ± 8</td>
<td>77.22 ± 7</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**Table 1. Baseline demographic, clinical and laboratory characteristics of the group A and B patients**

**Discussion**

The results of this study show that TNF-α blockers may reduce cIMT values in RA patients steadily responsive to therapy, provided that cases at high cardiovascular risk are excluded, thus allowing to speculate that extinguishing inflammation is the main mechanism by which TNF-α blockers may improve early ATS changes. The significant correlation found between cIMT and DAS₄₄ further strengthens such a hypothesis.

Ultrasonographic measurement of cIMT is a non-invasive, precise and reliable method for assessing early ATS vascular wall lesions. Increased cIMT value not only reflects local changes, but also corresponds to generalized ATS, as demonstrated by its strong connection with histological signs of coronary ATS [23, 24]. In RA patients, cIMT has been proven to be significantly higher than that observed in healthy controls matched for age, sex and classic cardiovascular risk factors [7], thus suggesting that chronic inflammatory state of active RA is an additional independent risk factor for accelerated ATS [25–29]. Further strengthening of this hypothesis is the observation of a close relationship between acute-phase protein levels and cIMT not only in RA patients, but also in healthy subjects [29].

Inflammation and immune cell activation have been demonstrated to play a key role in the pathogenesis of both ATS and RA [1]. A similar expansion of CD4+ T-cell subset that completely lacks the expression of the CD28 molecule has been found both in peripheral blood of patients with active RA [30], as well as in peripheral blood and coronary artery extracts of subjects with unstable angina [31]. CD4+ CD28− represents a T-lymphocyte

**Table 2. Results of the prospective analysis of mean values recorded at months 3, 6, 12 vs 0 within each group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Months</th>
<th>Group A Mean ± S.D.</th>
<th>Group B Mean ± S.D.</th>
<th>P&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS₄₄</td>
<td>0</td>
<td>5.64 ± 1.09</td>
<td>5.54 ± 1.18</td>
<td>0.0001</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>0</td>
<td>14.79 ± 13.90</td>
<td>14.76 ± 9.12</td>
<td>0.0001</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>0</td>
<td>31.67 ± 18.88</td>
<td>30.40 ± 12.55</td>
<td>0.0001</td>
</tr>
<tr>
<td>L-cIMT (mm)</td>
<td>0</td>
<td>0.63 ± 0.13</td>
<td>0.77 ± 0.13</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Table 3. Results from the statistical analysis of group A vs group B delta values at 12 months**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A Mean ± S.D.</th>
<th>Group B Mean ± S.D.</th>
<th>P&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS₄₄</td>
<td>5.54 ± 1.18</td>
<td>5.42 ± 1.37</td>
<td>0.62 ± 0.14</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>14.76 ± 9.12</td>
<td>13.78 ± 9.54</td>
<td>0.260</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>30.40 ± 12.55</td>
<td>29.10 ± 8.90</td>
<td>0.78 ± 0.15</td>
</tr>
<tr>
<td>L-cIMT (mm)</td>
<td>0.77 ± 0.13</td>
<td>0.77 ± 0.13</td>
<td>0.564</td>
</tr>
</tbody>
</table>

**Discussion**

The results of this study show that TNF-α blockers may reduce cIMT values in RA patients steadily responsive to therapy, provided that cases at high cardiovascular risk are excluded, thus allowing to speculate that extinguishing inflammation is the main mechanism by which TNF-α blockers may improve early ATS changes. The significant correlation found between cIMT and DAS₄₄ further strengthens such a hypothesis.

Ultrasonographic measurement of cIMT is a non-invasive, precise and reliable method for assessing early ATS vascular wall lesions. Increased cIMT value not only reflects local changes, but also corresponds to generalized ATS, as demonstrated by its strong connection with histological signs of coronary ATS [23, 24]. In RA patients, cIMT has been proven to be significantly higher than that observed in healthy controls matched for age, sex and classic cardiovascular risk factors [7], thus suggesting that chronic inflammatory state of active RA is an additional independent risk factor for accelerated ATS [25–29]. Further strengthening of this hypothesis is the observation of a close relationship between acute-phase protein levels and cIMT not only in RA patients, but also in healthy subjects [29].

Inflammation and immune cell activation have been demonstrated to play a key role in the pathogenesis of both ATS and RA [1]. A similar expansion of CD4+ T-cell subset that completely lacks the expression of the CD28 molecule has been found both in peripheral blood of patients with active RA [30], as well as in peripheral blood and coronary artery extracts of subjects with unstable angina [31]. CD4+ CD28− represents a T-lymphocyte

**Table 2. Results of the prospective analysis of mean values recorded at months 3, 6, 12 vs 0 within each group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Months</th>
<th>Group A Mean ± S.D.</th>
<th>Group B Mean ± S.D.</th>
<th>P&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS₄₄</td>
<td>5.54 ± 1.18</td>
<td>5.42 ± 1.37</td>
<td>0.62 ± 0.14</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>14.76 ± 9.12</td>
<td>13.78 ± 9.54</td>
<td>0.260</td>
<td></td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>30.40 ± 12.55</td>
<td>29.10 ± 8.90</td>
<td>0.78 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>L-cIMT (mm)</td>
<td>0.77 ± 0.13</td>
<td>0.77 ± 0.13</td>
<td>0.564</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

The results of this study show that TNF-α blockers may reduce cIMT values in RA patients steadily responsive to therapy, provided that cases at high cardiovascular risk are excluded, thus allowing to speculate that extinguishing inflammation is the main mechanism by which TNF-α blockers may improve early ATS changes. The significant correlation found between cIMT and DAS₄₄ further strengthens such a hypothesis.

Ultrasonographic measurement of cIMT is a non-invasive, precise and reliable method for assessing early ATS vascular wall lesions. Increased cIMT value not only reflects local changes, but also corresponds to generalized ATS, as demonstrated by its strong connection with histological signs of coronary ATS [23, 24]. In RA patients, cIMT has been proven to be significantly higher than that observed in healthy controls matched for age, sex and classic cardiovascular risk factors [7], thus suggesting that chronic inflammatory state of active RA is an additional independent risk factor for accelerated ATS [25–29]. Further strengthening of this hypothesis is the observation of a close relationship between acute-phase protein levels and cIMT not only in RA patients, but also in healthy subjects [29].

Inflammation and immune cell activation have been demonstrated to play a key role in the pathogenesis of both ATS and RA [1]. A similar expansion of CD4+ T-cell subset that completely lacks the expression of the CD28 molecule has been found both in peripheral blood of patients with active RA [30], as well as in peripheral blood and coronary artery extracts of subjects with unstable angina [31]. CD4+ CD28− represents a T-lymphocyte
subset with high pro-inflammatory and tissue damage potential, that has been observed to produce chemokines and cytokines in the early phases of RA and ATS [30]. Cytokines, chemokines and specific receptors, in turn, amplify the inflammatory process and contribute to the pathogenesis of a number of inflammatory diseases [32]. In particular, elevated CC family chemokine ligand 2 (CCL2) levels have been found in both synovial fluid of RA patients and ATS lesions, thus suggesting a common inflammatory pathway in RA and ATS. Possible favourable results from phase 1 and 2 clinical trials for the treatment of RA with CC family chemokine receptors 1 and 2 (CCR1 and CCR2, respectively) antagonists, which have also been implied in the pathogenesis of ATS so much to be proposed for its treatment [32], could provide further support to such an association.

Among the pro-inflammatory cytokines, TNF-α-plasma concentrations have been directly related to the degree of early carotid ATS [33]. It has been demonstrated that high levels of circulating TNF-α not only induce joint inflammation [34], but are also able to down-regulate the CD28 molecule expression on CD4+ T-lymphocytes [30] and to stimulate chemokine production [31]. Furthermore, TNF-α interferes with the lipoprotein metabolism [35], insulin sensitivity [27], coagulation system [27] and with the vascular generation of nitric oxide [36] and endothelium-derived hyperpolarizing factor [37], thus suggesting that persistent high levels of inflammatory mediators may induce an increased risk of developing cardiovascular disease. An altered lipoprotein pattern and the endothelial dysfunction are both considered key events in the early ATS development [1].

In the last 3 yrs, a growing body of literature has demonstrated that TNF-α blockers may have a protective effect against accelerated ATS, mainly related to their anti-inflammatory activity. In RA patients treated with TNF-α blockers, indeed, a significant restoration of the endothelial function [11–13] and a significant increase of high-density lipoprotein-cholesterol (HDL-C) levels [14] with an accompanying reduction of disease activity, ESR and CRP levels have been described [11–14].

Despite blockade of a cytokine with a pleiotropic activity profile, such as TNF-α, may be considered effective against accelerated ATS, mainly related to their anti-inflammatory activity. In RA patients treated with TNF-α blockers, indeed, a significant restoration of the endothelial function [11–13] and a significant increase of high-density lipoprotein-cholesterol (HDL-C) levels [14] with an accompanying reduction of disease activity, ESR and CRP levels have been described [11–14].

In conclusion, it may be hypothesized that in patients with long-standing disease (mean disease duration 5.1 yrs), provided that traditional cardiovascular risk factors and inflammation, genetic factors may contribute to the ATS risk in RA patients. Moreover, HLA-DRB1 alleles have been demonstrated to influence severity and progression of RA, further strengthening the hypothesis of a common genetic link between RA severity and cardiovascular risk [45]. It has been demonstrated that ATS is a dynamic process with a natural trend to worsening, but also a possibility to reverse. A significant reduction in size of the coronary atheroma has been reported in patients treated with rosuvastatin 40 mg/daily [46]. Moreover, a significant decrease of cIMT values has been documented in obese children with substantial weight loss [47] as well as in subjects treated with pravastatin 40 mg/daily [48]. Mechanisms by which statins may impair the ATS risk profile are mainly related to the improvement in lipid pattern, but also to an inflammatory marker reduction [49, 50].

Recently, progression of subclinical ATS has been described in eight RA patients with a long-standing disease (mean disease duration 15.4 ± 6.1 yrs) who had maintained a high disease activity despite at least a 2-yr treatment (median 3 yrs) with a TNF-α blocker [15]. The authors suggest that age at RA onset and disease duration were the main factors contributing to the natural age-related progression of ATS [15]. Disease duration, indeed, has been strongly associated with increased cIMT values [5] and with the development of carotid plaques [9], thus suggesting that long-standing RA may lead to severe ATS disease and high risk of cardiovascular events. In the current study, instead, a protective effect of TNF-α blockers was observed against early ATS changes in a larger group of active RA patients with a lower disease duration (6.6 ± 5.1 yrs), provided that traditional cardiovascular risk factors were excluded and all the patients were steadily responsive to such therapy. The results here reported suggest that in steadily responsive RA patients with a not long-standing history of active disease, ATS changes may be early and potentially reversible. The observation that cIMT values in the nine non-responder patients showed a stable or worsening trend after 1 yr suggests that not the simple treatment with anti-TNF-α but the response to it in RA inflammation is linked to ATS improvement.

In conclusion, it may be hypothesized that in patients with active RA, traditional cardiovascular risk factors do not completely account for the extent of accelerated ATS, but additional mechanisms, directly linked to the inflammatory process, should likely be postulated [29, 51]. Moreover, genetic factors should not be forgotten [45]. The results here reported show a significant reduction of cIMT values in highly selected patients, who had obtained an early and lasting significant reduction of DAS28, ESR and CRP values, thus confirming the
assumption on the pivotal role of inflammation in the pathogenesis of accelerated ATS in active RA patients.

The authors have declared no conflicts of interest.

References

36. Maki-Petaja KM, Hall FC, Booth AB et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity which is reduced by anti-tumour necrosis factor-alpha therapy. Circulation 2006;114:1185–92.
45. Mora S, Ridker PM. Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)—can C-reactive protein be used to target statin therapy in primary prevention? Am J Cardiol 2006;97:334–41A.