

# Intima-media thickness evolution after treatment with infliximab in patients with rheumatoid arthritis

Pierpaolo Di Micco<sup>1,2</sup>  
Paola Ferrazzi<sup>1</sup>  
Luca Librè<sup>1</sup>  
Loredana Mendolicchio<sup>1</sup>  
Ilaria Quaglia<sup>1</sup>  
Monica De Marco<sup>1</sup>  
Anna Colombo<sup>1</sup>  
Monica Bacci<sup>1</sup>  
Lidia Luciana Rota<sup>1</sup>  
Corrado Lodigiani<sup>1</sup>

<sup>1</sup>Thrombosis Center, Istituto Clinico Humanitas, Rozzano (MI), Italy;  
<sup>2</sup>Internal Medicine, Fatebenefratelli Hospital of Naples, Italy

**Background:** Atherosclerosis is a well known progressive disease that recognizes risk factors such as diabetes, hypertension, smoking, dyslipidemia, and inflammation. Mechanisms underlying atherosclerotic processes during inflammation are not completely understood, but cytokines are also involved, in particular tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Chronic inflammatory diseases such as rheumatoid arthritis (RA) are commonly associated with atherosclerotic complication. Little is known about the role of treatment of chronic inflammatory disease on the evolution of atherosclerosis in this kind of disease. Usually, evolution of atherosclerosis is monitored by intima-media thickness and the presence of plaques on several arteries such as common carotid.

**Aim:** The aim of the study was to monitor atherosclerosis evolution in seven RA patients on common treatment with infliximab (an anti-TNF- $\alpha$  drug) compared with seven RA patients during common treatment but not treated with infliximab.

**Patients and methods:** We selected 14 patients with RA according to the American College of Rheumatology classification criteria. Seven patients were selected before and after common treatment for RA based on nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate, and steroids (12 months), and seven patients before and after treatment based on infliximab associated with NSAIDs, methotrexate, and steroids (12 months). Ultrasound vascular imaging was performed to screen intima-media thickness and the presence of atherosclerotic plaques on common carotid artery and identify evolution of atherosclerosis.

**Results:** After 12 months, patients that were treated with infliximab showed significant worsening of atherosclerosis with an increase of intima-media thickness and the presence of further atherosclerotic plaques compared to patients that were treated traditionally and showed a nonsignificant increase of the same parameters.

**Discussion:** Treatment based on anti-TNF- $\alpha$  such as infliximab shows a worsening evolution of atherosclerosis based on our data. If these data are associated with a poor clinical outcome such as atherothrombosis of cerebral vessels and/or coronary vessels, this should be evaluated by further studies.

**Keywords:** atherosclerosis, infliximab, rheumatoid arthritis, intima-media thickness

## Background

Atherosclerosis is a well known progressive disease with risk factors that were recognized by the Framingham study (ie, aging, hypercholesterolemia, hypertension, diabetes, smoking, and family history of atherothrombosis).<sup>1</sup> Recently inflammation has been recognized as an additional atherosclerotic risk factor.<sup>2</sup> Mechanisms underlying atherosclerotic processes during inflammation are not completely understood, but increased production of reactive oxygen species (ROS) seems to be involved and

Correspondence: Pierpaolo Di Micco  
Internal Medicine, Fatebenefratelli  
Hospital of Naples, via san giacomo dei  
capri 69-80131 – Naples, Italy  
Email pdimicco@libero.it

seems to negatively interfere with reverse cholesterol transport and triggering atherosclerotic processes.<sup>3-5</sup>

Chronic inflammatory diseases such as rheumatoid arthritis (RA) are frequently associated with accelerated atherosclerosis<sup>6</sup> and with severe clinical presentations.<sup>7</sup> Moreover, several markers of inflammation such as C-reactive protein (CRP) are frequently increased in patients with atherosclerosis. On the other hand, any cytokine is increased during inflammation and are involved in atherosclerotic processes. Some authors report increased levels of several cytokines during RA such as intercellular adhesion molecule-1 (ICAM-1), interleukin-6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>8-10</sup>

It is still unknown whether treatment of inflammatory disease may improve the prognosis of atherosclerotic complication in patients with RA. In particular, data about the evolution of atherosclerosis in patients with RA taking ongoing anti-TNF- $\alpha$  drugs such as infliximab are lacking.

This article evaluates the atherosclerotic evolution of patients with RA on ongoing treatment with infliximab compared to patients on ongoing common treatment by the evaluation of intima-media thickness (IMT) and/or the presence of atherothrombotic plaques on common carotid with ultrasound imaging.

## Patients and methods

### Patients

We selected 14 consecutive patients affected by RA according to the American College of Rheumatology classification criteria. Patients were randomly divided into two different groups and assigned to two different treatment programs: group A included patients selected for therapy based on treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) on demand, steroids (*per os*, daily), methotrexate (intramuscular, weekly), and infliximab (3 mg/kg at time 0 and every eight weeks for one year); group B acted as a control group and included patients selected for common treatment based on NSAIDs on demand, steroids (*per os*, daily), and methotrexate (intramuscular, weekly).

Group A included seven patients (six females and one male; median age, 56 years), while group B included seven patients (six females and one male; median age, 53 years).

### Atherosclerosis evolution

Identification of atherosclerosis was performed with ultrasound imaging with a 7–10 Mhz linear probe (Vivid 4; GE Milan, Milan, Italy) in order to detect atherosclerotic plaques and the presence and the evolution of IMT.

Ultrasound imaging was performed at the beginning of treatment (time 0) and after 12 months (time 1) of treatment for both groups.

Detection of IMT was performed three times on common carotid of both sides at the origin and at the bulb for all patients according to guidelines suggested by the Italian Society for Angiology and Vascular Medicine. The median value of three detections was considered as the main value.

The imaging evaluation was performed as a double-blind evaluation by two different physicians.

### Clinical score

Disability related to RA for all patients was monitored according to the Health Assessment Questionnaire (HAQ) disability index<sup>11,12</sup> and Disease Activity Score using 28 joint counts (DAS 28)<sup>11,12</sup> at the beginning and at the end of treatment (ie, time 0 and time 1).

### Laboratory prognostic markers

Values of CRP were analyzed at time 0 and time 1 in order to have a laboratory follow-up screening of the evolution of RA in all selected patients in both groups.

### Statistical analysis

Statistical analysis was performed with Student's *t*-test for paired data. Data were considered to be significant if *p* value was < 0.05.

## Results

Our results are summarized in Table 1. We found an improvement of clinical score (ie, DAS 28) in both groups at time 0 and time 1, which was statistically significant (*p* = 0.04 and *p* = 0.003, respectively).

Neither differences nor improvements were found in both groups for disability score (ie, HAQ) at time 0 and time 1, which was statistically nonsignificant (*p* = 0.3 and *p* = 0.3, respectively).

Levels of CRP were similar in both groups at time 0 and time 1, which was statistically nonsignificant (*p* = 0.8 and *p* = 0.1, respectively).

Patients from group A being treated by ongoing infliximab and common therapy (NSAIDs, steroids, and methotrexate), showed worsening IMT at time 1 compared to time 0, which was statistically significant, while patients from group B showed light worsening of IMT at time 1 compared to time 0 and this value was not statistically significant.

**Table I** Clinical, imaging and laboratory follow up of patient with RA

	Group A			Group B			Normal values
	Time 0	Time 1	p	Time 0	Time 1	p	
IMT (mm)	0.84 ± 0.27	1.17 ± 0.39	0.026, s	1.07 ± 0.25	1.13 ± 0.24	0.2, ns	<0.07
DAS 28	7.0 ± 1.4	4.8 ± 2.0	0.04, s	6.4 ± 1.25	4.9 ± 1.96	0.003, ns	
HAQ	1.78 ± 0.75	1.41 ± 0.67	0.3, ns	1.36 ± 0.64	1.11 ± 0.74	0.3, ns	
PCR (mg/dL)	2.54 ± 1.99	2.42 ± 2.79	0.8, ns	2.16 ± 2.10	1.45 ± 2.05	0.1, ns	0.0–1.0

**Abbreviations:** DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; IMT, intima-media thickness; ns, not significant; PCR, polymerase chain reaction; RA, rheumatoid arthritis.

## Discussion

Patients affected by RA are more at risk of developing myocardial infarction and/or ischemic stroke when compared to the general population<sup>13,14</sup> because the presence of chronic inflammation associated with the possible presence of further atherothrombotic risk factors such as hypertension, diabetes, smoking, dyslipidemia, and family history of atherothrombosis. In recent years several biological drugs have been associated with common treatment of chronic inflammatory disease such as RA, based on NSAIDs, steroids, and methotrexate.<sup>15</sup> Prognosis, evaluated by disability and activity score, seems to be better for patients who have added biological drugs (ie, infliximab, etanercept, adalimumab, anakinra, etc)<sup>16</sup> to traditional therapy.

Infliximab, an anti-TNF- $\alpha$  drug, is one of the most common biological drugs used for the treatment of RA.<sup>16</sup> Treatment based on the administration of infliximab showed several improvements in the prognosis of RA, in particular advantages were found in several reports for disability index (eg, HAQ) and also for the disease activity score (eg, DAS 28).<sup>16</sup> Improvements were discovered not only on the global assessment, on the evolution of pain, and on fatigue, but also for serological markers such as improvement of CRP levels and for the improvement of endothelial dysfunction.<sup>17–19</sup> However, several side effects of treatment based on infliximab were reported. A higher risk *a priori* of infection development<sup>20,21</sup> has been underlined by several reports as the risk of recurrence of herpes zoster.<sup>22</sup> Furthermore, from a cardiovascular point of view, several side effects have been reported for patients in ongoing treatment with infliximab such as congestive heart failure<sup>23,24</sup> and an unassociated improvement of arterial stiffness.<sup>16</sup>

Data about the evolution of atherosclerosis for patients in ongoing treatment with infliximab are lacking in the literature. Our data showed an improvement of clinical parameters evaluated with the DAS 28 score for both

groups with RA. On the other hand, no different values were discovered in both groups when we consider the disability index (ie, HAQ) and CRP levels at times 0 and 1. Further data regarding the clinical follow-up of chronic inflammatory disease are lacking in our study and this aspect may be considered as a partial study limitation.

However, the aim of our study is to focus on the evolution of the atherosclerosis in patients with RA treated or untreated with infliximab. Interestingly, patients with RA treated with infliximab showed worsening of asymptomatic atherosclerosis analyzed by IMT and increasing evidence of atherosclerotic plaques while the increase of IMT for patients with RA treated with traditional drugs (ie, without infliximab) was slight. We may speculate that the worsening of atherosclerosis in group A may be related to the possible influence of other traditional atherosclerotic risk factors that have not been considered in our report. However, although data on the influence of traditional atherosclerotic risk factors are lacking and actually should be considered as a study limitation, we should consider two further relevant aspects: first of all, we should relate this aspect to the altered metabolism of lipoprotein during treatment with infliximab that has been reported in the literature,<sup>25,26</sup> but we may also consider that the natural history of RA, in particular its mortality, seems to be influenced mainly by atherothrombosis.<sup>27</sup> Therefore, for this reason, patients treated with infliximab may show a more advanced increase in IMT and asymptomatic plaques. We may speculate on the adverse cardiovascular outcome of such patients with RA treated with infliximab and this could also be in agreement with previous reports that reported an increased incidence of heart failure during treatment. It is not clear whether this aspect of treatment based on infliximab may be a class effect or a dose-dependent effect or may be associated with an increased incidence of atherothrombosis of in any vascular region is not clear and should be evaluated by further prospective studies focusing on the incidences of thrombotic events.

## Disclosure

The authors report no conflicts of interest in this work.

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