

Effects of Adalimumab Treatment on Vascular Disease Associated with Early Rheumatoid Arthritis

György Kerekes MD¹, Pál Soltész MD PhD¹, Gabriella Szűcs MF PhD², Szilvia Szamosi MD PhD², Henriett Dér MD PhD¹, Zoltán Szabó MD PhD², László Csáthy MD³, Andrea Vánca MD², Peter Szodoray MD PhD⁴, Gyula Szegedi MD PhD DSc⁵ and Zoltán Szekanecz MD PhD DSc²

¹Cardiovascular Unit, Third Department of Medicine, and ²Department of Rheumatology, Institute of Medicine, University of Debrecen Medical and Health Science Center, Debrecen, Hungary

³Department of Clinical Biochemistry and Molecular Pathology, University of Debrecen Medical and Health Science Center, Debrecen, Hungary

⁴Immunobiological Laboratory, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

⁵Autoimmune Research Group, Hungarian Academy of Sciences, Debrecen, Hungary

ABSTRACT: **Background:** Increased cardiovascular morbidity has become a leading cause of mortality in rheumatoid arthritis (RA). Tumor necrosis factor-alpha (TNFα) inhibitors may influence flow-mediated vasodilation (FMD) of the brachial artery, common carotid intima-media thickness (ccIMT) and arterial stiffness indicated by pulse-wave velocity (PWV) in RA.

Objectives: To assess the effects of adalimumab treatment on FMD, ccIMT and PWV in early RA.

Methods: Eight RA patients with a disease duration ≤ 1 year received 40 mg adalimumab subcutaneously every 2 weeks. Ultrasound was used to assess brachial FMD and ccIMT. PWV was determined by arteriograph. These parameters were correlated with C-reactive protein, von Willebrand factor (vWF), immunoglobulin M (IgM)-rheumatoid factor (RF), anti-CCP levels and 28-joint Disease Activity Score (DAS28).

Results: Adalimumab therapy successfully ameliorated arthritis as it decreased CRP levels ($P = 0.04$) and DAS28 ($P < 0.0001$). Endothelial function (FMD) improved in comparison to baseline ($P < 0.05$). ccIMT decreased after 24 weeks, indicating a mean 11.9% significant improvement ($P = 0.002$). Adalimumab relieved arterial stiffness (PWV) after 24 weeks. Although plasma vWF levels decreased only non-significantly after 12 weeks of treatment, an inverse correlation was found between FMD and vWF ($R = -0.643$, $P = 0.007$). FMD also inversely correlated with CRP ($R = -0.596$, $P = 0.015$). CRP and vWF also correlated with each other ($R = 0.598$, $P = 0.014$). PWV and ccIMT showed a positive correlation ($R = 0.735$, $P = 0.038$).

Conclusions: Treatment with adalimumab exerted favorable effects on disease activity and endothelial dysfunction. It also ameliorated carotid atherosclerosis and arterial stiffness in patients with early RA. Early adalimumab therapy may have an important role in the prevention and management of vascular comorbidity in RA.

KEY WORDS: rheumatoid arthritis, adalimumab, endothelial dysfunction, atherosclerosis, carotid intima-media thickness, arterial stiffness

Accelerated atherosclerosis, as well as increased cardiovascular morbidity and mortality have been associated with rheumatoid arthritis [1-5]. RA is an independent risk factor for accelerated cardiovascular disease [2-4]. Classical, Framingham, as well as inflammatory factors have been implicated in RA-related CVD [1-8]. Among the traditional risk factors, dyslipidemia, smoking and metabolic syndrome have been implicated in the development of atherosclerosis in RA [2,3,8]. Dyslipidemia in RA may be secondary to chronic inflammation [2,3]. Regarding inflammatory mechanisms, both atherosclerotic plaques and the RA synovium contain inflammatory leukocytes, mainly macrophages and T cells, pro-inflammatory cytokines including tumor necrosis factor-alpha, chemokines, matrix-degrading proteases and other inflammatory mediators [1-3,7-9]. It has been suggested that sustained inflammatory activity may be the predominant risk factor for accelerated atherosclerosis and excessive CVD mortality in RA [1-4,9].

Several ultrasonographic techniques have been developed to assess early vascular changes in RA. Accelerated atherosclerosis indicated by increased common carotid intimal-medial thickness has been described in RA [1-4]. As previously reported by us and others, early endothelial dysfunction indicated by

FMD = flow-mediated vasodilation

ccIMT = common carotid intima-media thickness

PWV = pulse-wave velocity

RA = rheumatoid arthritis

CRP = C-reactive protein

vWF = von Willebrand factor

CVD = cardiovascular disease

impaired endothelium-dependent flow-mediated vasodilation of the brachial artery precedes atherosclerosis in RA [1-4,10]. In addition, increased arterial stiffness indicated by increased pulse-wave velocity has also been associated with RA [10-12]. The detection of endothelial dysfunction, arterial stiffness or overt atherosclerosis is crucial for the early prevention and management of arthritis-related vascular disease.

The severity and outcome of CVD may also depend on disease duration in RA as atherosclerosis becomes more evident with the progression of the disease [1,2]. Most of the studies on vascular dysfunction, atherosclerosis and CVD were performed in long-lasting established RA [1,2,5]. There are only a few reports on early RA.

As described above, uncontrolled inflammation may be a key risk factor of CVD in RA [2-4,7,9]. Thus, as recently recommended by a EULAR task force, "adequate control of disease activity is necessary to lower the CVD risk." Also, most available evidence confirms that methotrexate and possibly biological agents may have beneficial effects on the vasculature in RA [13]. Indeed, numerous recent publications have suggested that biological agents, primarily TNF α inhibitors, may have significant effects on dyslipidemia, endothelial dysfunction, carotid atherosclerosis, arterial stiffness, and probably CVD outcome in RA [14-18]. In addition, two recent studies have reported similar beneficial effects of rituximab [19,20].

Most of the data have been published with respect to infliximab, and again, most studies have been performed in established rather than early RA [15-17]. Many groups reported favorable effects of TNF blockers on ccIMT or arterial stiffness [12,16,17]. However, there may be differences in the effects of different TNF α blockers. With regard to the few studies on the vascular effects of adalimumab, in one study eight RA patients refractory to infliximab were treated with adalimumab. There was a rapid increase of FMD on day 2, which was sustained for 12 weeks. This was accompanied by decreases in DAS28 and CRP levels [18].

Since there have been very few studies on the vascular effects of biologics in early RA and because little data are available on adalimumab, in the present study we assessed brachial FMD, an indicator of endothelial dysfunction, ccIMT, a marker of atherosclerosis, and PWV, an indicator of arterial stiffness in eight early RA patients undergoing adalimumab therapy. Since endothelium-independent nitroglycerine-mediated vasodilation was normal in our previous study [1], we did not assess this parameter.

PATIENTS AND METHODS

Our study group comprised eight early RA patients: 6 women and 2 men with a mean age of 37.8 years (range 24-69) [Table

Table 1. Patient characteristics at baseline

Patient no.	Gender	Age (yrs)	Disease duration (mos)	CCP	X-ray erosion	CRP	DAS28
1	M	69	6	+	-	36.4	6.72
2	F	47	12	+	-	25.2	5.76
3	F	29	3	-	-	7.5	5.35
4	F	25	4	+	-	156.4	7.22
5	F	25	7	+	-	120.0	6.42
6	M	24	3	-	-	56.1	5.21
7	F	36	2	+	+	19.0	6.02
8	F	47	8	+	-	2.0	5.12

CCP = cyclic citrullinated peptide, CRP = C-reactive protein, DAS28 = 28-joint Disease Activity Score

1]. The duration of disease was at least 1 year in all patients; the mean duration was 5.6 months (range 3-12 months) [Table 1]. None of the patients had ever received methotrexate or any biologics, and none had taken corticosteroids for at least 3 months prior to the study. According to the protocol, all patients received 40 mg adalimumab subcutaneously every 2 weeks. Concomitant methotrexate therapy of 10-15 mg/week was initiated in all patients. Exclusion criteria included known cardiovascular and cerebrovascular conditions, hypertension (blood pressure > 140/90 mmHg), diabetes mellitus, cigarette smoking, obesity (body mass index \geq 30 kg/m²), rheumatoid vasculitis, current infectious disease or renal failure (serum creatinine \geq 117 mmol/L).

All patients were fasting and had not used alcohol, tobacco, antioxidants or vasoactive drugs for 24 hours before the assessments. In addition, none of the RA patients received aspirin, clopidogrel, heparin or warfarin. Since this was a self-controlled study no control group was evaluated. The study was performed in accordance with the Helsinki Declaration. Informed consent was obtained from each patient and we also obtained approval from the local ethical committee at the University of Debrecen.

ASSESSMENT OF BRACHIAL ARTERY FMD

Brachial artery FMD was assessed as described previously [1]. Briefly, ultrasound examination was performed on the right arm using a 10-MHz linear array transducer (HP Sonos 5500) by a trained sonographer in a temperature-controlled room after the patient had rested for 30 minutes (basal value for FMD). A B-mode longitudinal section was obtained of the brachial artery above the antecubital fossa. In order to assess FMD, reactive hyperemia was induced by release of a pneumatic cuff around the forearm inflated to suprasystolic pressure for 4.5 minutes. After deflation the maximal flow velocity and the arterial diameter were recorded continuously for 90 minutes. The baseline diameter and FMD were elec-

trocardiographically gated and detected offline. FMD values were expressed as percent change from baseline (resting) value. Since endothelial function may change rather rapidly, FMD values were assessed at baseline (before the first injection) and then after 2, 4, 8 and 12 weeks. Although there is no generally accepted normal range for FMD, FMD < 5% may be considered as definitely impaired [1].

DETERMINATION OF COMMON CAROTID IMT

The ccIMT measurements were carried out as described [1]. Briefly, a duplex ultrasound system (HP Sonos 5500, 10 MHz linear array transducer) was used to assess the common carotid arteries by a single observer. Longitudinal high-resolution B-mode ultrasound scan was used in both right and left common carotid arteries and R-synchronized and recorded. The offline measurements were performed 1 cm proximal to the carotid bulb in the far wall. The ccIMT was defined as the distance between the first and second echogenic lines from the lumen, taking the average of 10 measurements on both sides. ccIMT values were expressed in mm. Since a relatively longer time is needed to detect changes in carotid atherosclerosis, ccIMT values were assessed at baseline (before the first injection) and after 24 weeks. Although there is no generally accepted normal range for ccIMT, an increase in ccIMT of at least 0.1 mm may be considered definitely abnormal [1].

ASSESSMENT OF ARTERIAL STIFFNESS

Measurements were carried out using a Tensioclinic arteriograph system (Tensiomed Kft., Debrecen, Hungary). This technique has recently been standardized and validated in RA and other rheumatic diseases [11,21]. The principle of this method is based on the fact that contraction of the myocardium initiates pulse waves in the aorta. The first wave becomes reflected from the aortic wall at the bifurcation; therefore, a second, reflected wave appears as a late systolic peak. The morphology of this second reflected wave depends on the stiffness of the large artery, the reflection time at 35 mmHg suprasystolic pressure of the brachial artery (RT S35), and the peripheral resistance-dependent amplitude.

Pulse wave velocity is the quotient of the jugular fossa-symphysis distance and RT S35 in m/s. The jugular fossa-symphysis distance is anatomically identical with the distance between the aortic trunk and the bifurcation. In order to have reproducible results, the patient needs to rest for at least 5 minutes before the assessment. In addition, the investigation room should be quiet. As more time is needed to observe changes in stiffness parameters, PWV was assessed at baseline and after 24 weeks.

LABORATORY ANALYSES

Circulating von Willebrand factor antigen is a marker of endothelial cell activation. Plasma levels of vWF were determined by STA Liatest vWF immunoturbidimetric assay using

microlatex particles coated with polyclonal rabbit anti-human vWF antibodies (Diagnostica Stago, Asnieres, France). After mixing the reagent with plasma, the degree of agglutination was proportional to the amount of vWF present in the plasma sample. The reference range was 50–160%. In this study, plasma vWF was assessed at baseline and after 2, 4, 8 and 12 weeks.

Serum IgM RF and CRP were assessed by quantitative nephelometry (Cobas Mira Plus-Roche, USA) using RF and CRP reagents, respectively (both Dialab). RF levels > 50 IU/ml and high-sensitivity CRP levels > 5 mg/L were considered elevated. Anti-cyclic citrullinated peptide autoantibodies were detected in serum samples using Immunoscan-RA CCP2 enzyme-linked immunosorbent assay test (Euro Diagnostica, Arnhem, The Netherlands). The assay was performed according to the manufacturer's instructions. A concentration > 25 IU/ml was considered positive.

DATA ANALYSIS AND REPRODUCIBILITY

To determine the effects of adalimumab on vascular function and dyslipidemia, a self-controlled study was designed. In order to compare different mean FMD, ccIMT, PWV or vWF values at different time points, percentages of change between any time point (b) and baseline (a) were calculated as follows: (b-a)/a x 100. Increased FMD and decreased ccIMT or PWV indicate improvement.

Since there were only eight patients in this pilot study, a limited statistical analysis could be performed using the SPSS software version 15.0. In case of normal distribution, differences were assessed by Student's paired *t*-test. Correlation analysis was performed by Pearson's test and *R* values were determined. In all analyses *P* values < 0.05 were considered significant.

Regarding reproducibility, all assessments were performed by a single observer (G.K.) Intra-observer variability of FMD, ccIMT and PWV measurements were calculated as 5%, 4.2% and 3.3%, respectively. The "stability" of measurements is indicated by the reproducibility for month-to-month repeated assessments of FMD, ccIMT or PWV. According to the Brand-Altman analysis, the 95% limits of agreement ranged between -1.6% and 1.9% for all assessments.

RESULTS

CLINICAL RESPONSE OF PATIENTS TO ADALIMUMAB

Eight patients with disease duration ≤ 12 months were included in the study. As described in Table 1, six patients were anti-CCP positive. After 12 weeks of adalimumab therapy, CRP levels significantly decreased from 52.8 ± 36.1 to 8.3 ± 5.0 mg/L (*P* = 0.04) (data not shown). In addition, DAS28 also significantly decreased from 5.98 ± 0.76 to 2.54 ± 0.53 (*P* < 0.0001) (data not shown). Anti-CCP and RF concentrations did not change with

anti-CCP = anti-cyclic citrullinated peptide

adalimumab therapy (data not shown). At baseline, only one patient had erosive disease, and no other patients developed erosions until week 24 (data not shown).

FLOW-MEDIATED VASODILATION

To assess endothelial function, brachial artery FMD was measured by high-resolution ultrasonography [Figure 1]. FMD improved in all patients as early as week 2. Figure 1 shows the mean absolute values of FMD at baseline and at weeks 2, 4, 8 and 12. Although the patient number did not permit detailed statistical analysis, mean (\pm SD) FMD values were $7.0 \pm 5.9\%$, $10.6 \pm 3.2\%$, $11.1 \pm 4.2\%$, $11.9 \pm 5.1\%$ and $13.2 \pm 5.6\%$, respectively. This indicated 51.4%, 58.6%, 70.0% and 88.6%, all significant improvements at weeks 2, 4, 8 and 12 in comparison to baseline, respectively ($P < 0.05$ at all time points).

CAROTID INTIMA-MEDIA THICKNESS

Although atherosclerosis may be a more prolonged process in comparison to endothelial dysfunction and improvement in ccIMT cannot be expected in the short term, when assessing ccIMT by ultrasonography we could detect notable changes after 24 weeks of treatment in comparison to baseline [Figure 2]. Again, ccIMT improved in all patients by week 24. As

Figure 1. Mean values of FMD (% dilation) at baseline and at weeks 2, 4, 8 and 12. Asterisk indicates significant ($P < 0.05$) difference as compared to baseline

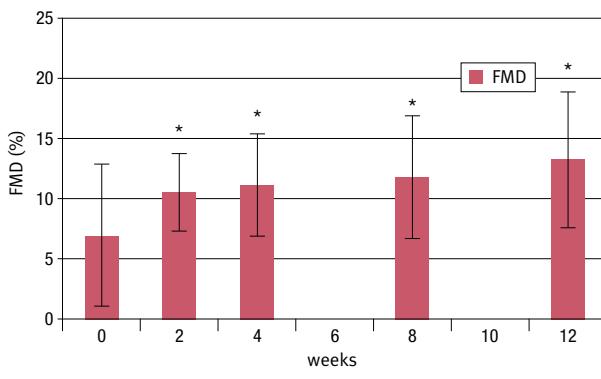
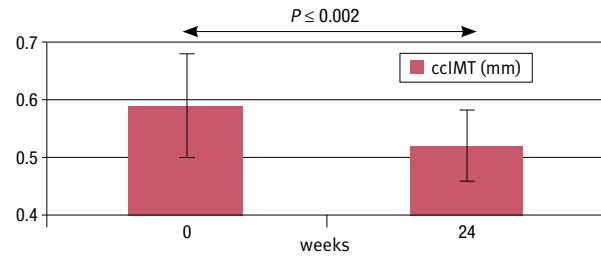


Figure 2. Mean values of ccIMT at baseline and week 24. There is a significant improvement in ccIMT



shown in Figure 2, the mean (\pm SD) ccIMT values at baseline and week 24 were 0.59 ± 0.09 mm and 0.52 ± 0.06 mm, respectively. This indicated a 11.9% significant improvement at week 24 in comparison to baseline ($P = 0.002$).

ARTERIAL STIFFNESS

We detected notable changes in PWV after 24 weeks of treatment compared to baseline. Adalimumab reduced PWV by week 24 in 4 of the 8 patients (50%). There was no change in PWV in one patient, while PWV increased in 3/8 patients (data not shown in figures).

The mean (\pm SD) PWV values at baseline and week 24 were 5.86 ± 1.85 m/s and 5.46 ± 1.52 m/s, respectively. This indicated a 6.8% non-significant improvement at week 24 in comparison to baseline (data not shown in figures).

PLASMA vWF LEVELS

We assessed circulating vWF levels as indicators of endothelial activation. Plasma vWF decreased in 5/8 patients by as early as week 2. By week 12, plasma vWF levels decreased in 6/8 patients (data not shown in figures).

The mean (\pm SD) plasma vWF levels at baseline and weeks 2, 4, 8 and 12 were $225.8 \pm 89.3\%$, $225.3 \pm 79.5\%$, $197.4 \pm 66.5\%$, $185.6 \pm 66.0\%$ and $184.8 \pm 60.3\%$, respectively. This indicated 0.2%, 12.6%, 17.8% and 18.2% decreases at weeks 2, 4, 8 and 12 in comparison to baseline, respectively, but these changes did not reach statistical significance (data not shown).

CORRELATIONS BETWEEN VASCULAR AND LABORATORY PARAMETERS

There was a significant inverse correlation between FMD and CRP ($R = -0.596$, $P = 0.015$) [Figure 3A]. Although, as presented above, adalimumab only non-significantly decreased plasma vWF levels, we also found a negative correlation between FMD and plasma vWF ($R = -0.643$, $P = 0.007$) [Figure 3B]. Interestingly, CRP and vWF also correlated with each other ($R = 0.598$, $P = 0.014$) [Figure 3C]. These results indicate that endothelial dysfunction may be associated with systemic inflammation, as well as endothelial activation. PWV and ccIMT showed a positive correlation ($R = 0.735$, $P = 0.038$) [Figure 3D], confirming that arterial stiffness is a consequence of atherosclerosis. No other correlations were significant (data not shown).

DISCUSSION

Accelerated atherosclerosis, as well as increased cardio- and cerebrovascular morbidity and mortality have been associated with RA [1-5,22,23]. Sustained systemic inflammation as well as traditional risk factors are major contributors to atherogenesis. Vasoprotective agents may be administered to

prevent and treat vascular conditions in RA; however, they primarily treat traditional Framingham risk factors [2-5,7]. Apart from methotrexate, biologics, mainly anti-TNF α agents, effectively suppress arthritis and exert various effects on the vascular system [5]. Short-term administration of infliximab, and possibly other biologics, may improve endothelial function, but in most cases the effect is transient [15]. There are far less data available on the effects of TNF α inhibitors on carotid atherosclerosis and arterial stiffness [16,17,22,23].

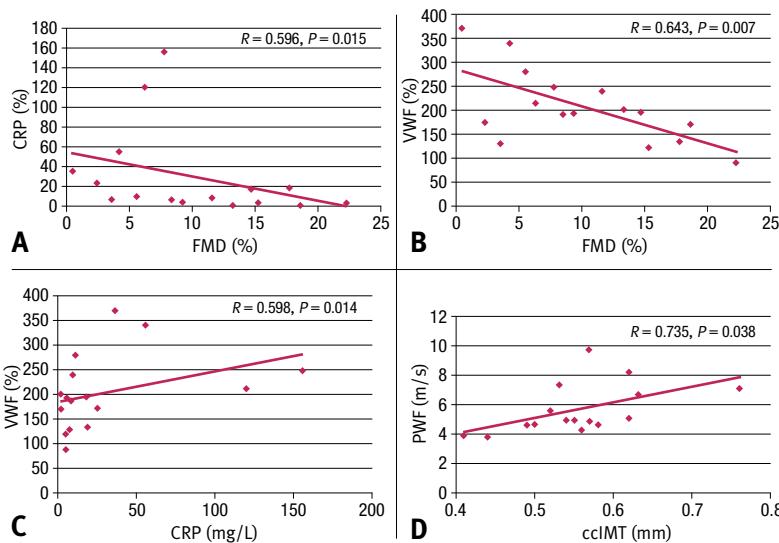
Hardly any data are available with respect to adalimumab. In one study, eight RA patients refractory to infliximab were treated with adalimumab. There was a rapid increase of FMD on day 2, which was sustained for 12 weeks. This was accompanied by decreases in DAS28 and CRP levels [18].

Since there is no report in which the vascular effects of adalimumab were investigated in early RA, we assessed eight patients with early RA who had a mean age of 36 years and a mean disease duration of 9 months. We assessed FMD, ccIMT, PWV and plasma vWF levels at different time points during adalimumab therapy. Early adalimumab treatment resulted in a significant amelioration of FMD by as early as 2 weeks in all patients. FMD increased by more than 50%, and by week 12 reached 88%. Circulating vWF is a marker of endothelial activation. In this study, adalimumab treatment decreased plasma vWF levels by 13–18% between weeks 4 and 12 in most patients. Improvement of FMD correlated with decreases of both CRP and vWF production, suggesting that endothelial dysfunction, systemic inflammation and endothelial activation may be closely related to each other.

We did not find reports on the possible effects of adalimumab treatment on carotid atherosclerosis, arterial stiffness or circulating vWF levels in early or long-lasting RA. Here ccIMT significantly improved in all patients by 12% after 24 weeks of treatment. Although significant changes in ccIMT are usually observed after months, surprisingly, we observed improvement of ccIMT as early as 24 weeks of therapy. In most available studies, ccIMT was measured only after a year of treatment. It is possible that early changes in FMD and metabolic parameters may translate into decreased ccIMT as early as 24 weeks. In our study on rituximab, ccIMT declined even earlier [20]. Arterial stiffness indicated by PWV also showed a non-significant (7%) improvement by week 24 in half of the patients. In addition, ccIMT and PWV correlated with each other, indicating that atherosclerosis may be the essential factor in arterial stiffness.

When assessing the effects of biologics on vascular disease outcome, the age- and gender-adjusted incidence rate of first CVD events was less than half in anti-TNF-treated patients compared with untreated ones [24]. When data from the British Society for Rheumatology Biologics Register were recently analyzed, there was no difference in the incidence of myocardial infarction between patients treated with biologics

Figure 3. Significant correlations between vascular and laboratory markers. There are inverse correlations between FMD versus CRP [A] and vWF [B]. There are positive correlations between CRP and vWF [C], as well as between ccIMT and PWV [D]



and those who were not. However, when anti-TNF responders and non-responders were compared, the risk of infarction was markedly reduced in patients exhibiting a good clinical response after 6 months of anti-TNF therapy as compared to non-responders [25]. Adalimumab therapy has not yet been assessed in this respect.

In conclusion, early adalimumab therapy may improve endothelial function and may postpone the development of atherosclerosis and arterial stiffness in RA patients. Since cardiovascular disease is a major mortality factor in RA and sustained systemic inflammation is the key mechanism in the pathogenesis of arthritis-related atherosclerosis, biological therapy, such as adalimumab, may have relevance for the prevention and management of vascular co-morbidity in RA. Further investigations are needed to determine the long-term effects of adalimumab, as well as other biologics, on the vasculature in inflammatory diseases such as RA.

Acknowledgments:

This work was supported by research grant T 048541 (Z.S.) and a Bolyai Research Grant (P.S.)

Corresponding author:

Dr. Z. Szekanecz

Institute of Medicine, Dept. of Rheumatology, University of Debrecen Medical and Health Science Center, Móricz Zs krt. 22., H-4032 Debrecen, Hungary
email: szekanecz.zoltan@med.unideb.hu

References

- Kerekes G, Szekanecz Z, Dézsi H, et al. Endothelial dysfunction and atherosclerosis in rheumatoid arthritis: a multiparametric analysis using imaging techniques and laboratory markers of inflammation and autoimmunity. *J Rheumatol* 2008;

- 35: 398-406.
2. Giles JT, Post W, Blumenthal RS, Bathon JM. Therapy insight: managing cardiovascular risk in patients with rheumatoid arthritis. *Nature Clin Pract Rheumatol* 2006; 2: 320-9.
 3. Shoenfeld Y, Gerli R, Doria A, et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. *Circulation* 2005; 112: 3337-47.
 4. Szekanecz Z, Kerekes G, Dér H, et al. Accelerated atherosclerosis in rheumatoid arthritis. *Ann NY Acad Sci* 2007; 1108: 349-58.
 5. Kerekes G, Soltész P, Dér H, et al. Effects of biologics on vascular function and atherosclerosis associated with rheumatoid arthritis. *Ann NY Acad Sci* 2009; 1173: 814-21.
 6. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; 340: 115-26.
 7. Szekanecz Z. Pro-inflammatory cytokines in atherosclerosis. *IMAJ Isr Med Assoc J* 2008; 10: 529-30.
 8. Chung CP, Oeser A, Solus JF, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. *Atherosclerosis* 2008; 196: 756-63.
 9. Kaplan MJ. Cardiovascular disease in rheumatoid arthritis. *Curr Opin Rheumatol* 2006; 18: 289-97.
 10. Wällberg-Jonsson S, Caidahl K, Klintland N, Nyberg G, Rantapää-Dahlqvist S. Increased arterial stiffness and indication of endothelial dysfunction in long-standing rheumatoid arthritis. *Scand J Rheumatol* 2008; 37: 1-5.
 11. Soltész P, Dér H, Kerekes G, et al. A comparative study of arterial stiffness, flow-mediated vasodilation of the brachial artery and the thickness of carotid artery intima-media in patients with systemic autoimmune diseases. *Clin Rheumatol* 2009; 28: 655-62.
 12. Mäki-Petäjä KM, Hall FC, Booth AD, et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor- α therapy. *Circulation* 2006; 114: 1185-92.
 13. Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010; 69: 325-31.
 14. Gonzalez-Gay MA, Garcia-Unzueta MT, De Matias JM, et al. Influence of anti-TNF-alpha infliximab therapy on adhesion molecules associated with atherogenesis in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2006; 24: 373-9.
 15. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, Garcia-Porrúa C, Llorca J, Gonzalez-Gay MA. Active but transient improvement of endothelial function in rheumatoid arthritis patients undergoing long-term treatment with anti-tumor necrosis factor α antibody. *Arthritis Rheum* 2004; 51: 447-50.
 16. Del Porto F, Lagana B, Lai S, et al. Response to anti-tumour necrosis factor α blockade is associated with reduction of carotid intima-media thickness in patients with active rheumatoid arthritis. *Rheumatology* 2007; 46: 1111-15.
 17. Wong M, Oakley SP, Young I, et al. Infliximab improves vascular stiffness in patients with rheumatoid arthritis. *Ann Rheum Dis* 2009; 68: 1277-84.
 18. Gonzalez-Juanatey C, Llorca J, Sanchez-Andrade A, Garcia-Porrúa C, Martin J, Gonzalez-Gay MA. Short-term adalimumab therapy improves endothelial function in patients with rheumatoid arthritis refractory to infliximab. *Clin Exp Rheumatol* 2006; 24: 309-12.
 19. Gonzalez-Juanatey C, Llorca J, Vazquez-Rodriguez TR, Diaz-Varela N, Garcia-Quiroga H, Gonzalez-Gay MA. Short-term improvement of endothelial function in rituximab-treated rheumatoid arthritis patients refractory to tumor necrosis factor α blocker therapy. *Arthritis Rheum (Arthritis Care Res)* 2008; 59: 1821-4.
 20. Kerekes G, Soltész P, Dér H, et al. Effects of rituximab treatment on endothelial dysfunction and lipid profile in rheumatoid arthritis. *Clin Rheumatol* 2009; 28: 705-10.
 21. Baulmann J, Schillings U, Rickert S, et al. A new oscillometric method for assessment of arterial stiffness: comparison with tonometric and piezo-electronic methods. *J Hypertens* 2008; 26: 523-8.
 22. Sherer Y, Gerli R, Gilburd B, et al. Thickened carotid artery intima-media in rheumatoid arthritis is associated with elevated anticardiolipin antibodies. *Lupus* 2007; 16: 259-64.
 23. Gerli R, Sherer Y, Bocci EB, et al. Precocious atherosclerosis in rheumatoid arthritis: role of traditional and disease-related cardiovascular risk factors. *Ann NY Acad Sci* 2007; 1108: 372-81.
 24. Jacobsson LT, Turesson C, Gülfé A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol* 2005; 32: 1213-18.
 25. Dixon WG, Watson KD, Lunt M, Hyrich KL; British Society for Rheumatology Biologics Register Control Centre Consortium, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2007; 56: 2905-12.