RHEUMATOLOGY

Concise report

Automated radiofrequency-based US measurement of common carotid intima–media thickness in RA patients treated with synthetic *vs* synthetic and biologic DMARDs

Esperanza Naredo[1], Ingrid Möller[2], Alfonso Corrales[3], David A. Bong[2], Tatiana Cobo-Ibáñez[4], Hector Corominas[5], Ma Luz Garcia-Vivar[6], Pilar Macarrón[7], Teresa Navio[8], Patricia Richi[4], Annamaria Iagnocco[9], Jesús Garrido[10] and David Martínez-Hernández[11]

Abstract

Objective. To compare the carotid intima–media thickness (IMT) assessed with automated radiofrequency-based US in RA patients treated with synthetic *vs* synthetic and biologic DMARDs and controls.

Methods. Ninety-four RA patients and 94 sex- and age-matched controls were prospectively recruited at seven centres. Cardiovascular (CV) risk factors and co-morbidities, RA characteristics and therapy were recorded. Common carotid artery (CCA)-IMT was assessed in RA patients and controls with automated radiofrequency-based US by the same investigator at each centre.

Results. Forty-five (47.9%) RA patients had been treated with synthetic DMARDs and 49 (52.1%) with synthetic and biologic DMARDs. There were no significant differences between the RA patients and controls in demographics, CV co-morbidities and CV disease. There were significantly more smokers among RA patients treated with synthetic and biologic DMARDs ($P = 0.036$). Disease duration and duration of CS and synthetic DMARD therapy was significantly longer in RA patients treated with synthetic and biologic DMARDs ($P < 0.0005$). The mean CCA-IMT was significantly greater in RA patients treated only with synthetic DMARDs than in controls [591.4 (98.6) *vs* 562.1 (85.8); $P = 0.035$] and in RA patients treated with synthetic and biologic DMARDs [591.4 (98.6) *vs* 558.8 (95.3); $P = 0.040$]. There was no significant difference between the mean CCA-IMT in RA patients treated with synthetic and biologic DMARDs and controls ($P = 0.997$).

Conclusion. Our results suggest that radiofrequency-based measurement of CCA-IMT can discriminate between RA patients treated with synthetic DMARDs *vs* RA patients treated with synthetic and biologic DMARDs.

Key words: ultrasound, carotid intima–media thickness, rheumatoid arthritis, radiofrequency.

CLINICAL SCIENCE

[1]Department of Rheumatology, Hospital General Universitario Gregorio Marañón and Complutense University, Madrid, [2]Department of Rheumatology, Instituto Poal, Barcelona, [3]Department of Rheumatology, Hospital de Valdecilla, Santander, [4]Department of Rheumatology, Hospital Universitario Infanta Sofía, Madrid, [5]Department of Rheumatology, Hospital Moisès Broggi de Sant Joan Despí, Barcelona, [6]Department of Rheumatology, Hospital Basurto, Bilbao, [7]Department of Rheumatology, Hospital Clínico San Carlos, Madrid, [8]Department of Rheumatology, Hospital Universitario Infanta Leonor, Madrid, Spain, [9]Department of

Rheumatology, Sapienza Università di Roma, Rome, Italy, [10]Department of Social Psychology and Methodology Faculty of Psychology, Autónoma University of Madrid and [11]Department of Preventive Medicine and Public Health, Faculty of Medicine, Complutense University of Madrid, Madrid, Spain.

Correspondence to: Esperanza Naredo, Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Dr Alvarez Sierra 4, 4° A, 28033 Madrid, Spain. E-mail: enaredo@ser.es

Introduction

There is a body of evidence that supports the pathogenic role of chronic inflammation in atherosclerosis [1–5]. This condition and its consequent cardiovascular (CV) events are largely responsible for the increased morbidity and mortality risk in RA patients [6–10].

Intima–media thickness (IMT) of the common carotid artery (CCA) measured by B-mode US is increasingly used as a valid non-invasive surrogate marker of athero-sclerosis and an end point of CV disease, independent of traditional CV risk factors, in observational and interventional studies [11–14]. In RA patients, increased CCA-IMT assessed by US has shown independent predictive value in relation to both subclinical atherosclerosis and CV events [15, 16].

In different RA populations with early or established disease, and with and without classical CV risk factors, a significantly increased CCA-IMT has been demonstrated as compared with matched controls [5, 17–23]. Two systematic literature reviews and meta-analyses have reinforced this evidence [24, 25]. CCA-IMT correlated positively with disease duration and clinical and laboratory parameters of inflammatory activity on the one side [17, 18, 21–23] and with age and traditional CV risk factors on the other side [17, 18, 21, 23] in previously published studies. Some studies have reported that the suppression of inflammation by biologic therapies (e.g. TNF blocking agents) has a protective effect against developing atherosclerosis and CV events [26–30].

In the above literature, the CCA-IMT was measured online or offline from B-mode images by manual, semi-manual or automated detection of the lumen–intima and media–adventitia interfaces over an artery segment [31]. These methods are highly machine and operator dependent, require substantial specific training, and can be time consuming. US technology based on radiofrequency provides an automated method for measuring carotid IMT, which is uninfluenced by the B-mode image quality and less dependent on the experience in vascular US of the examiner [32].

We have previously demonstrated multi-examiner reproducibility and feasibility of automated radiofrequency-based CCA-IMT measurement performed by rheumatologists in RA patients [33]. In addition, the above method has shown good agreement with the conventional B-mode US measurement of CCA-IMT [33–35].

The objective of this multicentre study was to compare the CCA-IMT measured by automated radiofrequency-based US in RA patients treated with synthetic *vs* synthetic and biologic DMARDs and controls.

Methods

Study population

Ninety-four patients with RA according to the ACR 1987 criteria [36], who consecutively attended the outpatient rheumatology clinics, and 94 sex- and age-matched controls were prospectively recruited at seven centres.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethical committee of the involved centres (Hospital General Universitario Gregorio Marañón, Spain; Instituto Poal, Spain; Hospital de Valdecilla, Spain; Hospital Universitario Infanta Sofía, Spain; Hospital Moisès Broggi de Sant Joan Despí, Spain; Hospital Basurto, Spain; Hospital Clínico San Carlos, Spain; Hospital Universitario Infanta Leonor, Spain). Written informed consent was obtained from all patients before the study.

Clinical and laboratory assessment

The following demographic and clinical data were recorded for each RA patient and control at study enrolment: age, sex and history of CV risk factors and diseases. Each subject was questioned about the following co-morbidities and CV risk factors: hypertension, diabetes mellitus, dyslipidaemia, renal insufficiency, obesity, hyperuricaemia or gout, peripheral atherosclerotic arterial disease, coronary artery disease or events, cerebrovascular events, family history (i.e. first-grade relatives) of early (<50 years) CV events, and current or past smoking habit. These co-morbidities were defined according to published criteria [16] (see supplementary data, available at *Rheumatology* Online). In addition, the following data were recorded for RA patients: disease duration and CSs, synthetic and biologic DMARDs received for RA.

RA patients and controls underwent clinical assessment at study entry that consisted of systolic blood pressure (SBP) and diastolic blood pressure (DBP), waist circumference (at the level of the cranial edge iliac crest) and BMI. RA activity was estimated by calculating the DAS in 28 joints (DAS28) for each RA patient. Functional ability was evaluated with a self-assessment Spanish version of the HAQ. ESR (normal 10–20 mm/h), CRP (normal 0–10 mg/l), RF (normal 0–15 IU/ml) and ACPA (normal 0–20 U) were also obtained at study enrolment.

Automated radiofrequency-based US measurement of CCA-IMT

CCA-IMT was assessed in both RA patients and controls by the same investigator at each centre, blinded to clinical and laboratory data, with seven commercially available real-time scanners (i.e. five MyLab 25 Gold and two Mylab 70; Esaote, Genoa, Italy) equipped with 7–12 MHz linear transducers and the same automated software-guided technique, RF-Quality Intima Media Thickness (QIMT; Esaote, Maastricht, Holland). These investigators were expert in musculoskeletal (MS) US and had demonstrated good inter- and intra-observer reliability in measuring CCA-IMT in RA patients [33].

IMT was measured at the posterior wall of the right and left CCA, 10 mm from the carotid bifurcation over the proximal 15-mm long segment. The patients were placed in the supine position with their heads slightly bent to the opposite direction of the examination side. The right CCA was first identified in B-mode in a transverse view and followed from the proximal part to the bulb origin. Immediately after, the CCA and the most proximal

part of the bulb were imaged in a longitudinal view from a lateral approach (supplementary Fig. S1, available as supplementary data at *Rheumatology* Online). The QIMT software was enabled by pressing a specific button at the scanner keyboard. A 15-mm long region of interest (ROI) and a reference line on the left were superimposed on the B-mode image. The vertical reference line was placed on the bulb origin. The distance between this line and the left margin of the ROI was 10 mm. The ROI was positioned so that a marker in the middle of the reference line was located in the centre of the artery lumen. The mean and s.D. of the IMT values from the last six cardiac cycles were continuously calculated by the system and displayed on the left side of the image. According to the manufacturers, the s.D. should be <20 μm to maximize the quality and accuracy of the IMT measurements. As soon as the s.D. was <20 μm for the first time during the measurement process, the investigators froze the image and collected the mean IMT value for analysis. The QIMT values were expressed in micrometres (supplementary Fig. S2, available as supplementary data at *Rheumatology* Online). This procedure was repeated on the left CCA.

Statistical analysis

Statistical analysis was performed using SPSS, version 15.0 (SPSS, Chicago, IL, USA). Quantitative variables were presented as the mean (s.D.) and range or median and interquartile range (Q_1–Q_3) depending on the normality assumption checked with the Kolmogorov–Smirnov test. Qualitative variables were summarized as absolute and relative frequencies. *T*-test or Mann–Whitney U-test was used to compare means between two independent samples depending on the assumptions for parametric tests, and one-factor analysis of variance (ANOVA) and *post hoc* Tukey test or Kruskal–Wallis test and Mann–Whitney U-test with Bonferroni correction to compare means between three independent samples. Pearson's χ^2-test and Fisher's exact test were used to compare frequencies. Correlations between quantitative variables were analysed by Pearson's correlation coefficient. $P<0.05$ was considered significant.

Results

Sample characteristics

The studied population comprised 188 subjects, 22 (11.7%) men and 166 (88.3%) women, 94 RA patients and 94 sex- and age-matched controls. Of the 94 RA patients, 45 (47.9%) had been treated with synthetic DMARDs (mainly MTX and LEF) and 49 (52.1%) with synthetic and biologic DMARDs (i.e. adalimumab, infliximab, etanercept, rituximab, tocilizumab, abatacept, golimumab, ofatumumab); 24 patients had received one biologic agent, 19 patients had received two biologic agents and 6 patients had received three biologic agents. Seventy-five (80%) patients had received systemic CSs. The control group comprised 86 volunteers without rheumatic diseases and eight patients with non-inflammatory rheumatic diseases (i.e. FM, two patients;

OA, two patients; rotator cuff tendinopathy, two patients; osteoporosis, one patient; mechanical dorsalgia, one patient).

Table 1 displays demographic, clinical and laboratory data for RA patients who had received only synthetic DMARDs, RA patients who had received synthetic and biologic DMARDs and controls. There were no significant differences between the three groups in demographics, CV co-morbidities, CV events and family history of CV disease. There were significantly more smokers among RA patients treated with synthetic and biologic DMARDs than among either, RA patients treated only with synthetic DMARDs or controls ($P=0.036$). Disease duration and duration of CS and synthetic DMARD therapy was significantly longer in RA patients treated with synthetic and biologic DMARDs than in RA patients treated only with synthetic DMARDs ($P<0.0005$). The median HAQ and the number (percentage) of positive ACPA patients were also significantly higher in RA patients who had received synthetic and biologic agents as compared with RA patients who had received only synthetic DMARDs ($P=0.029$ and $P=0.043$, respectively). There were no significant differences between both groups in DAS28, RF, ESR and CRP values.

CCA-IMT in RA patients and controls

CCA-IMT measurements ranged from 349 to 744 μm in the control group, from 377 to 851 μm in the RA group treated with synthetic DMARDs and from 300 to 773 μm in the RA group treated with synthetic and biologic DMARDs. CCA-IMT correlated significantly with age in the three groups. These correlations were as follows: $r=0.51$, $P<0.0005$ for controls; $r=0.49$, $P=0.001$ for RA patients treated with synthetic DMARDs; and $r=0.72$, $P<0.0005$ for RA patients treated with synthetic and biologic DMARDs. Table 2 displays CCA-IMT values for RA patients and controls. There were significant differences between the three groups ($P=0.023$). *Post hoc* Tukey's pairwise comparisons showed that the mean CCA-IMT was significantly greater in RA patients treated only with synthetic DMARDs than in controls ($P=0.035$). In addition, the mean CCA-IMT was significantly greater in RA patients treated only with synthetic DMARDs than in RA patients treated with synthetic and biologic DMARDs ($P=0.040$). There was no significant difference between the mean CCA-IMT in RA patients treated with synthetic and biologic DMARDs and controls ($P=0.997$).

Discussion

The growing body of evidence of increased CV risk in RA patients has led the rheumatology community to recognize the importance of this in clinical practice and research [5–10, 15, 16, 37]. Several CV scientific societies have reported that CCA-IMT assessment should be included in the routine assessment of CV risk [13, 37]. The criterion validity of CCA-IMT US measurement has been established in histological studies [38]. The added

TABLE 1 Demographic, clinical and laboratory data in RA patients who had received synthetic DMARDs, RA patients who had received synthetic and biologic DMARDs and controls

Clinical and laboratory data	RA patients treated with synthetic DMARDs (n = 45)	RA patients treated with synthetic and biologic DMARDs (n = 49)	Controls (n = 94)	P
Age, mean (S.D.), years	44.8 (9.2)	44.9 (8.5)	44.7 (8.7)	0.983
Sex, women, n (%)	39 (86.7)	44 (89.8)	83 (88.3)	0.895
BMI, mean (S.D.), kg/m^2	25.9 (5.2)	24.3 (3.7)	24.3 (4.3)	0.099
WC, mean (S.D.), cm	87.2 (12.6)	82.8 (11.6)	82.2 (11.8)	0.067
SBP, mean (S.D.), mmHg	122.2 (15.8)	119.2 (15.6)	117.0 (14.9)	0.171
DBP, mean (S.D.), mmHg	76.7 (10.0)	73.8 (8.8)	75.0 (9.0)	0.322
Hypertension, n (%)	5 (11.1)	6 (12.2)	10 (10.6)	0.959
Diabetes mellitus, n (%)	2 (4.4)	0 (0.0)	1 (1.1)	0.193
Dyslipidaemia, n (%)	11 (24.4)	9 (18.4)	11 (11.7)	0.153
Renal insufficiency, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Obesity, n (%)	4 (8.9)	4 (8.2)	7 (7.4)	0.956
Hyperuricaemia, n (%)	1 (2.3)	0 (0.0)	0 (0.0)	0.202
Gout, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
PAD, n (%)	0 (0.0)	0 (0.0)	1 (1.1)	0.605
CAD, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
CBE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
FH, n (%)	6 (13.3)	8 (16.7)	16 (17.2)	0.840
Smoking habit, n (%)				
Current	10 (22)	20 (41)	19 (20)	0.036
Past	8 (18)	11 (22)	16 (17)	
Never	27 (60)	18 (37)	59 (63)	
RA duration, median (Q$_1$–Q$_3$), months	48.0 (12.0–86.5)	84.0 (53.0–164.0)	NA	<0.0005
SDMARDs duration, median (Q$_1$–Q$_3$), months	10.0 (0.0–32.0)	40.5 (14.0–81.0)	NA	<0.0005
CSs duration, median (Q$_1$–Q$_3$), months	21.0 (8.0–58.0)	55.0 (25.0–146.3)	NA	<0.0005
BDMARDs duration, median (Q$_1$–Q$_3$), months	NA	32.0 (11.3–58.3)	NA	NA
DAS28, mean (S.D.), months	3.17 (1.39)	3.35 (1.36)	NA	0.536
HAQ, median (Q$_1$–Q$_3$)	0.37 (0.00–1.37)	0.88 (0.19–1.38)	NA	0.029
RF, n (%)	32 (72.7)	34 (70.8)	NA	0.840
ACPA, n (%)	24 (55.8)	35 (76.1)	NA	0.043
ESR, mean (S.D.), mm/h	17.9 (14.5)	23.0 (20.9)	NA	0.199
CRP, mean (S.D.), mg/l	4.6 (7.6)	5.4 (7.1)	NA	0.619

WC: waist circumference; PAD: peripheral atherosclerotic arterial disease; CAD: coronary artery disease or events; CBE: cerebrovascular events; FH: family history (i.e. first-grade relatives) of early (<50 years) CV events; SDMARDs: synthetic DMARDs; BDMARDs: biologic DMARDs; NA: not applicable.

TABLE 2 Vascular assessment (CCA-IMT) values in RA patients and controls

Vascular assessment	RA patients treated with synthetic DMARDs (n = 45)	RA patients treated with synthetic and biologic DMARDs (n = 49)	Controls (n = 94)	ANOVA P
CCA-IMT, mean (S.D.), μm	591.4 (98.6)	558.8 (95.3)	562.1 (85.8)	0.023

value of CCA-IMT in CV risk assessment has been shown also in RA patients [15, 16].

In our study we found a significantly greater CCA-IMT in RA patients treated with synthetic DMARDs than in sex- and age-matched controls who, in addition, did not show differences in CV risk factors and co-morbidities as compared with the above RA population. This result was in accordance with those of previous studies that compared RA patients receiving the above therapy with controls [5, 17, 18, 21–23]. Additionally, we found a significantly greater CCA-IMT in RA patients treated only with synthetic DMARDs than in RA patients treated with

synthetic and biologic DMARDs despite significantly longer disease duration, higher number of smokers and worse HAQ in this latter group. However, the CCA-IMT was comparable in the latter RA population and controls. This cross-sectional finding is consistent with the results of some longitudinal studies that have shown a significantly greater increase in CCA-IMT in RA patients receiving synthetic DMARDs as compared with RA patients receiving biologic therapy [28–30]. It can also be argued that the longer synthetic DMARDs and CS therapy might have contributed to the smaller CCA-IMT in patients treated with synthetic and biologic therapy. However, the influence of these treatments on the CCA-IMT has not been firmly elucidated [16, 39].

Some limitations in our study should be noted. The type of study, being cross-sectional, limited any prediction or causality assessment. In addition, the low prevalence of CV co-morbidities did not allow us to analyse their relation with the CCA-IMT in the studied populations.

In conclusion, our results suggest that radiofrequency-based measurement of CCA-IMT was able to discriminate between RA patients treated with synthetic DMARDs *vs* RA patients treated with synthetic and biologic DMARDs, and that biologic therapy may have a protective effect on the increased carotid IMT and atherosclerotic process widely described in the literature on RA patients. Further longitudinal studies on the long-term effect of synthetic and biologic treatment on carotid IMT are warranted.

> ### Rheumatology key messages
> - CCA-IMT was greater in RA patients on DMARDs as compared with those on biologic therapy.
> - Biologic therapy may have a protective effect on the atherosclerotic process in RA patients.
> - Implementation of carotid IMT in rheumatology practice may provide additional value to RA management.

Acknowledgements

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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