Clinical research

Treat-to-target therapy does not prevent excessive progression of carotid intima media thickness during the first year of therapy in early rheumatoid arthritis

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Abstract

Introduction: The aim of the study was to investigate the presence of subclinical atherosclerosis and predictors of change in carotid intima-media measures in early rheumatoid arthritis patients (eRA) as compared to chronic RA patients and patients without arthritis.
Material and methods: Fifty-five consecutive eRA patients were assessed at the time of diagnosis and after 1 year of therapy. Fifty-five sex- and age-matched chronic RA patients and 29 patients without inflammatory disease were used as controls. Carotid artery intima-media thickness (CIMT) and carotid plaques were measured at baseline and after follow-up. In eRA patients ultrasound assessment of hand joints was performed before and after treatment. Carotid artery intima-media thickness was assessed again after 2 years in 44 eRA patients.
Results: Carotid artery intima-media thickness progression after 1 year of therapy was higher in eRA patients compared to both control groups (p = 0.017) and correlated with symptoms duration (p = 0.017) and DMARD monotherapy (p = 0.015). Ultrasound progression of hand joint erosions was associated with longer symptoms duration (p = 0.006). After 2 years of observation CIMT progression was similar in all examined groups.
Conclusions: We observed rapid CIMT progression during the first year of RA therapy. Longer symptoms duration and less aggressive therapy were associated with CIMT increase.

Key words: atherosclerosis, rheumatoid arthritis, treatment.

Introduction

Rheumatoid arthritis (RA) patients have increased cardiovascular (CV) risk due to accelerated atherosclerosis compared to the general population [1]. Cardiovascular risk begins early and may precede RA diagnosis [2–4]. Ultrasound assessment of carotid artery intima-media thickness (CIMT) is a useful noninvasive tool to detect subclinical atherosclerosis [5–8]. Carotid artery intima-media thickness in RA is associated with traditional CV risk factors and with persistent systemic inflammation [9–13]. Effective therapy at the beginning of the disease plays a pivotal role in suppressing inflammation, joint damage and organ involvement.

The time just after RA onset is known as the window of opportunity to stop joint damage [14]. It is not clear if halting inflammation at an early stage of the disease has the same influence on premature atherosclerosis as on joint damage [15–17]. Some reports show that CIMT progression is faster at earlier stages of RA than in patients with established disease [18–20]. It is postulated that early treatment reduces subclinical atherosclerosis and CV risk in newly diagnosed RA patients [21]. Numerous studies have shown the positive role of disease-modifying antirheumatic drugs (DMARDs) in reducing CIMT progression in established RA [22–28]. The role of glucocorticosteroids (GCS) as a cause of CV risk in RA remains controversial. It is well known that GCS have negative effect on CV risk factors, but they may play a positive role acting as anti-inflammatory agents [29–31]. The aim of our study was to compare the prevalence of subclinical atherosclerosis and its progression measured by CIMT in early RA and chronic RA patients, and to investigate factors associated with CIMT progression during the first year of therapy.

The study was approved by the local ethical committee. Each participant signed an informed consent form. All procedures were performed in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Material and methods

Fifty-five consecutive early rheumatoid arthritis (eRA) patients were recruited at the time of diagnosis. The patients fulfilled the 2010 ACR/EULAR criteria [32] and had no known prior CV events. We defined eRA as disease duration ≤ 12 months in the absence of any antirheumatic therapy. A complete history, physical examination and laboratory evaluation were performed and recorded in a standard protocol (Table I). The patients were treated according to the treat-to-target protocol (assessment every month until low disease activity with steroids cessation was achieved). During

Table I. Demographic data and traditional CVD risk factors in eRA patients and two control groups, age- and sex-matched

Parameter	Baseline			Follow-Up		
	eRA (*N* = 55)	Control I (RA) (*N* = 55)	Control II (non RA) (*N* = 29)	eRA (*N* = 55)	Control I (RA) (*N* = 55)	Control II (non RA) (*N* = 29)
Women, *n* (%)	43 (78)	43 (78)	22 (76)	43 (78)	43 (78)	22 (76)
Age [years]	58.5 ±14	58.2 ±13	58.2 ±13	59.6 ±14	60.9 ±13	60.9 ±13
Hypertension, *n* (%)	29 (52.7)	25 (50)	12 (41.4)	30 (54.5)	31 (56)	13 (45)
Diabetes mellitus, *n* (%)	5 (9)	5 (9)	2 (7)	7 (12.7)	5 (9)	2 (7)
HbA_{1c} [mg/dl]	5.5 ±3	–	–	5.3 ±2.5	–	–
Chronic renal disease, *n* (%)	2 (3.6)	2 (3.6)	1 (3.5)	2 (3.6)	2 (3.6)	1 (3.5)
Serum creatinine [mg/dl]	0.7 ±0.14	0.73 ±0.27	0.71 ±0.1	0.78 ±0.18	0.74 ±0.26	0.75 ±0.1
Hypercholesterolemia, *n* (%)	25 (45.5)	30 (54.5)	17 (58.6)	28 (51)	30 (54.5)	17 (58.6)
HDL [mg/dl]	**51 ±15**	64 ±20	61 ±20	57 ±15	65 ±20	75 ±12
Cholesterol/HDL ratio	**3.9 ±1**	3.3 ±1	3.5 ±1	3.6 ±0.9	3.5 ±1.3	3.1 ±0.6
LDL cholesterol [mg/dl]	125 ±36	108 ±34	122 ±40	135.6 ±34	112 ±30.5	128 ±37
Triglycerides [mg/dl]	120 ±55	127 ±70	153 ±80	118 ±46	114 ±60	114.5 ±46
BMI [kg/m^2]	26.5 ±5	26.2 ±5	27.5 ±3	26.7 ±5	26 ±4.4	27 ±3
Smoking now, *n* (%)	**13 (23.6)**	7 (13)	2 (7)	12 (22)	7 (13)	2 (7)
Smoking ever, *n* (%)	27 (49)	25 (45)	**7 (13)**			
Pack-years	12 ±15	11 ±17	2 ±4	13 ±14	12 ±16	2.5 ±4
FRS 10-year risk score	6.2 ±6	4.3 ±3.7	4.9 ±5.4	6.2 ±5.8	4.5 ±4	4.1 ±5
Family history of CVD, *n* (%)	**11 (20)**	28 (51)	12 (41)			
Treatment with NSAID, *n* (%)	20 (36.4)	20 (36.4)	**3 (10.3)**	11 (20)	11 (20)	3 (10.3)
Treatment with statins, *n* (%)	2 (3.6)	9 (16)	3 (10.3)	4 (7)	9 (16)	3 (10.3)
Treatment with glucocorticosteroids, *n* (%)	49 (89)*	34 (62)	0	15 (27)	30 (54.5)	0

*Data are expressed as mean (standard deviation) or number of patients (percentage). Statistically significant differences are bolded. BMI – body mass index, CVD – cardiovascular disease, HbA_{1c} – glycated hemoglobin, FRS – Framingham 10-year risk score, NSAID – nonsteroidal anti-inflammatory drugs, eRA – early rheumatoid arthritis, RA – rheumatoid arthritis. *Glucocorticosteroids prescribed at baseline.*

the first year of therapy they were evaluated 6–11 times with clinical data and samples of blood collected at each visit. The number of tender and swollen joints (28 joint count) was evaluated by the same physician and the disease activity score (DAS28) including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) was calculated. X-rays of hands and feet were performed at baseline and after 12 ±2 months in eRA patients.

The first line treatment included methotrexate (MTX) or leflunomide (LEF), with prednisone. Twenty-five patients who did not achieve low disease activity (DAS28ESR < 3.2) after 3–6 months of treatment were given an additional DMARD: LEF (17 patients), sulfasalazine (SSA) (3 patients), or chloroquine (CQ) (5 patients). We defined combination therapy as treatment with more than one DMARD for a minimum of half the observation period. The cumulative dose of DMARDs and steroids was documented at each visit. We calculated the average doses by dividing the cumulative doses by the time of observation (Table II).

Controls I (RA)

We used data of 55 sex- and age-matched patients treated for RA for ≥ 1 year, without known CV disease, registered in the ongoing prospective study of CV risk in the same center (Table I). Thirty-one patients were given combination therapy and 24 received monotherapy (21 MTX, 2 LEF, and 1 CQ). Thirty-three (60%) of the patients were treated with prednisone (Table II).

Controls II

Twenty-nine controls without RA and without CV disease history were included in the study, of whom 27 were selected from healthy persons screened for allergy at the same center and 2 persons were recruited from the hospital staff. The controls (1 control for 2 patients, but in 3 cases 1 control per patient) were matched for age and sex.

Laboratory tests

Laboratory tests in eRA patients (except erythrocyte sedimentation rate (ESR), blood count, liver enzymes and C-reactive protein (CRP) measured at each visit) assessed at baseline and after 12 ±1 months included: serum concentration of creatinine, fasting glucose and lipid profile. The controls were assessed at baseline and after approximately 32 months. The laboratory examinations in control groups included: blood count, ESR, CRP, serum creatinine and lipid profile. IgM rheumatic factor (RF) and anti-cyclic citrullinated peptide antibodies (a-CCP) were measured in eRA and RA patients. Rheumatic factor was measured by immunonephelometry. Anti-CCP autoantibodies were measured by fluoroenzyme-immunoassay using the automated Unicap 100 system.

Ultrasound assessment

The carotid artery ultrasound examination (UE) was performed and interpreted by the same assessor using the protocol described elsewhere

Table II. Characteristics of disease duration, disease activity and treatment in eRA and RA patients. Only statistically significant differences are included

Variable	eRA	RA	*P*-value
Baseline disease/symptoms duration [years]	0.4 ±0.3	12 ±10.6	0.0001
Baseline ESR [mm/h]	54.6 ±25	30.2 ±19	0.0004
Baseline CRP median (quartiles) [mg/l]	31 (10–80)	13.3 (4–23)	0.001
Anti-CCP, *n* (%)	29 (52.7)	38 (69)	0.01
Baseline DAS28CRP	6 ±1	4.8 ±1.5	0.00001
Baseline DAS28ESR	5.75 ±1	5.09 ±1.5	0.01
Mean DAS28ESR	3.4 ±0.8	4.36 ±1.8	0.0009
Follow-up DAS28ESR improvement	2.6 ±1.5	1.4 ±1.5	0.0001
Follow-up DAS28CRP improvement	2.7 ±1.6	1.5 ±1.6	0.0001
Follow-up DAS28ESR remission, *n* (%)	23 (41.8)	13 (23.6)	0.04
Methotrexate mean dose [mg/week]	22.8 ±4.6	16.1 ±9	0.00006
Biologic DMARDs, *n* (%)	1 (1.8)	18 (32.7)	0.0004
Glucocorticosteroids, *n* (%)	50 (90.9)	33 (60)	0.02

Data are expressed as mean (standard deviation), median (quartiles) or number of patients (percentage). Anti-CCP – anti-citrullinated protein antibodies, CRP – C-reactive protein, DMARDs – disease-modifying antirheumatic drugs, ESR – erythrocyte sedimentation rate, DAS28 – disease activity score, eRA – early rheumatoid arthritis, RA – rheumatoid arthritis. ˙Medications used for ≥ 3 months are included.

[33]. Briefly, CIMT was measured on the far wall of the common carotid arteries. Carotid artery intima-media thickness was defined as a mean value of 6 measurements. In eRA patients the assessments were performed at baseline and after 1 year of therapy (±2 weeks). In 12 patients the assessment was performed later (18–24 months from the baseline). In these cases we calculated the yearly progression of CIMT by subtracting the baseline from the follow-up IMT and dividing by the time between two scans. Forty-four patients were assessed additionally after 24 months. In control groups the assessment was performed at baseline and after 24–32 months. We calculated yearly CIMT progression as described above. UE of hand joints was done only in eRA patients. All joint assessments were performed on the same Esaote MyLab ClassC (Esaote CA, USA) with a 6–18 MHz linear array transducer. We defined disease progression as an increase in the number of joints with erosions.

The Framingham 10-year risk score (FRS) was used to estimate general CV risk related to classical risk factors [34].

Statistical analysis

All statistical analyses were performed with Statistica 10.0 (StatSoft). Differences between groups were estimated by one-way ANOVA, independent or dependent sample *t*-test and Mann-Whitney *U* test, as appropriate. Categorical variables were compared with a χ^2 test. The correlation between variables was examined using Pearson's correlation coefficient or Spearman's correlation coefficient according to data distribution. Simple linear regression analysis was used to explore the predictive relationship between CIMT and CIMT progression and classical CVD risk factors, demographic variables and disease-specific variables. Simple linear regression determined co-variates included in the multiple regression models. Carotid artery intima-media thickness progression greater than the mean ± SD of the control II group (without RA) was defined as rapid progression. Logistic regression analysis was used to examine variables associated with rapid CIMT progression. *P*-values < 0.05 were considered statistically significant.

Results

There were no significant differences between eRA patients and controls in age, sex, body mass index (BMI) or comorbidities (Table I). There was a lower number of current and previous smokers and fewer nonsteroidal anti-inflammatory drugs (NSAID) users in the control II group (non-RA) than in patients with arthritis. At baseline eRA patients had a lower high density lipoprotein (HDL) cholesterol concentration (p = 0.0002) and higher cholesterol/HDL ratio (p = 0.003) than controls. The follow-up increase of serum HDL and decrease of total cholesterol/HDL ratio correlated inversely with ESR (β = –0.3, p = 0.03). Baseline inflammatory markers and disease activity indices were higher in eRA as compared to established RA (Table II).

The majority of eRA patients (63.6%) had no radiological abnormalities in hands and feet X-ray examinations at diagnosis; juxta-articular osteoporosis was found in 18 (32.7%) patients and marginal erosions were found in 2 (3.6%) patients. After 1 year juxta-articular osteoporosis was found in 19 (34.5%) radiographs and erosions in 6 (10.6%). On UE erosions were found in 9 (16.4%) of the eRA patients at baseline and in 16 (29%) patients at follow-up. New erosions were found in 13 (23.6%) of the patients. A significant difference in symptoms duration was found between the patients with and the patients without progression of erosions in UE (9.7 ±9 vs. 4.2 ±3 months respectively; p = 0.006).

The best predictors of baseline CIMT in eRA were GFR and FRS (R = 0.8), in control I (RA) age (R = 0.71), and in control II age and FRS (R = 0.85). The CIMT progression in eRA patients was higher than in controls (Table III). In all examined groups the relations between CIMT at second examination and CV risk factors remained similar to the first measurements (Table IV). In eRA patients

Table III. Carotid intima media thickness (CIMT) and presence of plaques in early RA patients and two control groups

Variable	eRA	Control I (RA)	Control II	*P*-value
Baseline CIMT [mm]	0.73 ±0.2	0.693 ±0.2	0.68 ±0.2	0.36
Follow-up CIMT [mm]	0.77 ±0.2	0.723 ±0.2	0.696 ±0.2	0.13
CIMT progression [mm]	0.046 ±0.05	0.03 ±0.034	0.02 ±0.02	0.017
Baseline plaques, *n* (%)	9 (16.4)	13 (23.6)	3 (10.3)	0.3
New plaques, *n* (%)	3 (5.4)	5 (10)	1 (3.6)	0.8

Data are expressed as mean (standard deviation) or number of patients (percentage). eRA – early rheumatoid arthritis, RA – rheumatoid arthritis.

follow-up CIMT correlated additionally with ESR, swollen joint count, baseline glycated haemoglobin (HbA_{1c}) and with prednisone dose and GCS treatment duration, but in the multiple regression model these correlations became insignificant.

We used the yearly rate of CIMT change in further analyses. In all examined groups the demographic, CV risk and disease-related factors did not show any relation with CIMT yearly progression. In eRA patients significant values were found for the symptoms duration, duration of GCS therapy and DMARD monotherapy. In a stepwise linear regression model CIMT progression in eRA patients correlated with duration of symptoms before treatment (β = 0.3 p = 0.017) and DMARD monotherapy (β = 0.3, p = 0.015) (R = 0.4). Taking the mean ± SD of the CIMT progression in the control II group (without RA) as the upper limit of the normal CIMT progression we defined a subgroup of patients with "rapid progression". There were 30 (54.5%) "rapid progressors" in eRA patients, 24 (43.6%) in RA patients and 6 (20.7%) in non-RA patients. RA patients (eRA + RA) were 3 times more likely to be "rapid progressors" than non-RA patients (OR = 2.9, p = 0.008). In eRA "rapid progressors" were characterized by older age, higher number of patients with joint erosions at baseline, longer symptoms duration, higher baseline HbA_{1c} and less aggressive treatment than "average progressors" (Table V). The stepwise logistic regression to identify factors associated with rapid CIMT progression selected symptoms duration, OR = 1.24 (95% CI: 1.02–1.5), p = 0.02 and combination DMARD therapy, OR = 0.2 (95% CI: 0.05–0.7), p = 0.01. We compared separately eRA and RA patients treated with monotherapy and combination therapy. In both eRA and RA groups the patients treated with combination therapy were younger and had slightly higher average disease activity than the patients treated with only one DMARD. The CIMT progression in combination therapy (25 eRA and 31 RA patients) was quite similar (0.028 ±0.05 mm in eRA and 0.025 ±0.03 mm in RA, p = 0.79), while in the monotherapy group (30 eRA and 24 RA patients) the early

Table IV. Simple linear regression model of correlations of follow-up carotid intima media thickness [mm] with traditional cardiovascular risk and disease-related factors. Only statistically significant values are included

Factor	eRA β	*P*-value	Control I (RA) β	*P*-value	Control II β	*P*-value
Age	0.7	0.000002	0.72	< 0.000001	0.5	0.005
Female sex	–0.27	0.03	–	–	–	
Serum creatinine	0.47	0.0002	–	–	0.65	0.01
GFR	–0.66	0.001	–	–	–0.7	0.01
Framingham score	0.55	0.0001	0.36	0.008	0.77	0.0004
Hypertension	0.42	0.001	0.3	0.01	–	–
HDL cholesterol	–	–	–	–	–0.5	0.006
Total cholesterol/HDL	–	–	–	–	0.54	0.003
Triglycerides	–	–	–	–	0.4	0.04
BMI	0.3	0.04	–		–	–
Serum uric acid	0.34	0.01	–		–	
Pack-years	0.3	0.02	0.3	0.04	–	–
Baseline HbA_{1c}	0.48	0.03	–		–	
Mean ESR	0.3	0.03	–		–	
Swollen joint count at follow-up	0.25	0.04	–		–	
Mean prednisone dose [mg/day]	–0.28	0.03	–		–	
Cumulative prednisone dose [mg/year]	–0.3	0.02	–		–	
Baseline CIMT	0.96	< 0.000001	0.98	< 0.000001	0.99	< 0.000001

ESR – erythrocyte sedimentation rate, DAS28 – disease activity score, GFR – glomerular filtration rate, HDL – high-density lipoprotein, eRA – early rheumatoid arthritis, RA – rheumatoid arthritis, HbA_{1c} – glycated hemoglobin.

Table V. Characteristics of 55 eRA patients according to observed progression in carotid intima-media thickness (CIMT). Only statistically significant associations are shown

Variable	CIMT progression > 0.037 mm (rapid progressors) *N* = 30	CIMT progression ≤ 0.037 mm *N* = 25	*P*-value
Baseline age [years]	63 ±12	52.8 ±15	0.006
Follow-up CIMT [mm]	0.84 ±0.19	0.69 ±0.19	0.006
Baseline HbA_{1c} [mg/dl]	5.78 ±0.4	5.2 ±0.5	0.009
Duration of RA symptoms [months]	7.6 ±8	3 ±2.6	0.008
Prednisone mean dose [mg/day]	3.9 ±3	6 ±4.5	0.03
Duration of glucocorticosteroids treatment [months]	5.8 ±3.7	7.8 ±4.4	0.04
Combination DMARD therapy, *n* (%)	8 (26.7)	17 (68)	0.003

Data are expressed as mean (standard deviation) or number of patients (percentage).

RA patients showed significantly higher CIMT progression (0.06 ±0.05 vs. 0.035 ±0.04, $p = 0.03$).

Forty-four eRA patients were additionally assessed after 24 months. The CIMT yearly progression was lower during the second year of therapy than during the first year (0.01 ±0.06 mm vs. 0.046 ±0.6 mm; $p = 0.02$) and similar to CIMT progression in control groups.

Discussion

Carotid artery intima-media thickness in untreated eRA is higher than in healthy individuals [12, 16, 20]. In our previous study in chronic RA patients receiving more aggressive treatment (high methotrexate (MTX) doses, cyclosporine or biologics) CIMT was lower as compared with the patients on low MTX doses [33]. Some studies demonstrated that standard treatment with MTX and prednisone or triple therapy (MTX + HQ + SSA) can stop CIMT progression during the first year of therapy [21, 35]. We tried to verify the hypothesis that early therapy inhibits CIMT changes. We included eRA patients with high disease activity and applied a strategy with strict control according to disease activity. Despite a good therapeutic effect, our study revealed rapid progression of CIMT during the first year. Comorbidities in eRA and control groups were similar, so the inclusion of unselected patients should not be the source of inconsistency. Dissimilarity between eRA and RA patients cannot be fully explained by use of biologic therapy in the RA group, because the significant difference in CIMT progression was found predominantly in the MTX monotherapy patients. A possible explanation is that traditional DMARDs are slow-acting drugs, so during the first months of treatment their anti-inflammatory action had not been achieved. We observed that longer symptoms duration before treatment was associated with CIMT progression and with new joint erosions. Presumably the 1-year period was too short to achieve complete inhibition of inflammation. In line with this assumption is our observation of a protective role of low GCS doses. In contrast to DMARDS, steroids are fast-acting drugs, so their anti-inflammatory action can be observed earlier. The acceleration of atherosclerosis in eRA may be an effect of a long-term inflammatory process preceding diagnosis. This could partially explain the lack of correlation with disease activity measures during the observation period. In our study significant correlations of CIMT were found only with ESR and swollen joint count. This is consistent with other studies. In observational studies CIMT progression was associated with swollen joint count, and not with other markers of disease activity [36, 37]. It seems that disease activity measures used in daily practice are not sufficient to be applied separately in CV risk assessment. A recent study of 487 RA patients showed that with the growing number of CV risk factors the association of CIMT with ESR has become stronger [12]. An earlier study also supports the hypothesis of interaction between traditional CV risk factors and inflammation in the atherogenic process [19]. In our study the patients with rapid CIMT progression were characterized by older age and less aggressive therapy but not higher disease activity. This may indicate that aggressive therapy should be considered at the beginning of the treatment in all RA patients. Another interesting finding in our study is the correlation of follow-up CIMT with baseline glycated hemoglobin concentration. It is consistent with suggestions from other studies that eRA patients are more likely to be insulin-resistant [38].

Among the limitations of our study, the study group was small and consisted of unselected con-

secutive eRA patients with a number of confounding comorbidities. The follow-up time was short, but it provided an opportunity to observe rapid vessel wall changes. In contrast to the majority of early RA studies we used ACR/EULAR 2010 criteria, which are more sensitive than the ACR 1987 criteria in detecting early arthritis, so we could observe the disease process at a really early stage. On the other hand, the inclusion of forms of arthritis other than RA was more likely.

In conclusion, we have found excessive progression of CIMT in early rheumatoid patients despite the tight disease activity control. Longer symptoms duration before treatment and DMARD monotherapy were associated with rapid CIMT progression. More aggressive treatment may reduce the risk of atherosclerosis in patients with early rheumatoid arthritis.

Conflict of interest

The authors declare no conflict of interest.

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