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Artículo original

Inflamación endotelial en pacientes con artritis reumatoide tratados con tofacitinib: un estudio observacional

Endothelial inflammation in patients with Rheumatoid Arthritis treated with Tofacitinib: an observational study

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Palabras clave: artritis reumatoide; tofacitinib; riesgo cardiovascular.

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RESUMEN

Introducción: la afectación cardiovascular es común en pacientes con artritis reumatoide (AR). El tofacitinib se ha asociado con un aumento de eventos cardiovasculares en algunos pacientes con AR. La tomografía por emisión de positrones con 18F-fluorodesoxiglucosa (PET-FDG/TC) es una prueba sensible y específica para evaluar la inflamación de la pared vascular.

Objetivos: evaluar la inflamación vascular endotelial usando PET-FDG/TC en pacientes con AR activa que iniciaron tratamiento con tofacitinib al inicio y después de 12 semanas de tratamiento.

Materiales y métodos: estudio observacional, prospectivo y multicéntrico. Se incluyeron pacientes consecutivos con AR de actividad moderada/alta, sin tratamiento previo con bDMARD, que iniciaban tofacitinib. Se evaluaron datos clínicos, actividad de la enfermedad y se realizó PET-FDG/TC al inicio y a la semana 12 de tratamiento con tofacitinib. La inflamación endotelial se evaluó utilizando SUVmax y TBRmax. Se realizó ecografía Doppler de las arterias carótidas al inicio y a la semana 12, y se midió el grosor de la íntima-media.

Resultados: se incluyeron 30 pacientes, 70% mujeres, mediana de edad 57,5 años (IQR 42-65), duración mediana de la AR 5 años (IQR 2-12), DAS28ESR mediana 5.24 (IQR 4.6-6.1), CDAI mediana 27.5 (IQR 20-34). A la semana 12 del tratamiento con tofacitinib, los pacientes mostraron una disminución significativa en la actividad de la enfermedad según DAS28ESR (5.21 versus 3.04; p<0,0001) y CDAI (26.6 versus 8.80; p<0,0001), pero la captación de 18F-FDG en las áreas evaluadas no mostró diferencias significativas entre el inicio y la semana 12, con todas las áreas vasculares exploradas mostrando un SUVmax por encima del umbral predefinido que define inflamación al inicio.

Conclusiones: en nuestro estudio no encontramos cambios en la inflamación vascular a la semana 12 del tratamiento con tofacitinib, a pesar de la mejoría en la actividad de la enfermedad.

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Key words: *rheumatoid arthritis; tofacitinib; cardiovascular risk.*

ABSTRACT

Introduction: *cardiovascular involvement is frequent in patients with rheumatoid arthritis (RA). The use of tofacitinib has been linked with an increase in cardiovascular events in some populations of RA patients. 18F-fluorodeoxyglucose Positron Emission Tomography (PET-FDG/TC) has emerged as a sensitive and specific test for the evaluation of vascular wall inflammation.*

Objectives: *evaluate the endothelial vascular inflammation using PET-FDG/TC in patients with active RA initiating tofacitinib at baseline and after 12 weeks of treatment.*

Materials and methods: *observational, prospective, multicentric study. Consecutive patients with RA with moderate/high activity, bDMARD-naive, who were to start tofacitinib were included. Clinical data, disease activity, and a PET-FDG/TC were performed at baseline and at week 12 of tofacitinib treatment. Endothelial inflammation was assessed using SUVmax and TBRmax. Carotid artery Doppler ultrasonography was performed at baseline and week 12, and intima-media thickness was measured.*

Results: *30 patients were included, 70% female, median age 57.5 (IQR 42-65) years old, median RA duration 5 (IQR 2-12) years, median DAS28ESR 5.24 (IQR 4.6-6.1), median CDAI 27.5 (IQR 20-34). At week 12 of tofacitinib treatment, patients showed a significant decrease in disease activity by DAS28ESR (5.21 vs 3.04, p<0.0001) and CDAI (26.6 vs 8.80, p<0.0001), but 18F-FDG uptake in the evaluated areas showed no significant difference between baseline and week 12, with all explored vascular showing a SUVmax over the prestipulated threshold defining inflammation at baseline.*

Conclusions: *In our study, we found no change in vascular inflammation at week 12 of tofacitinib treatment, despite improvement in disease activity.*
Key word: rheumatoid arthritis; tofacitinib; cardiovascular risk.

INTRODUCTION

Rheumatoid arthritis (RA) is the most frequent inflammatory arthritis worldwide, affecting 0.2-2% of the population in different cohort studies[1]. It is a multi-systemic immune-mediated disease with predominant damage to the synovial tissue, causing pain and deformity due to erosive bone destruction.

In RA, extra-articular manifestations and comorbidities are frequent and have an impact on long-term prognosis. In an observational study evaluating the prevalence of comorbidities in RA, cardiovascular events (CVE) were the third most frequent comorbidity, after depression and asthma[2]. Mayor CVEs were observed in 6% of patients in this study.

Mortality measured as the standardized mortality ratio (SMR) in patients with RA is higher than in the general population and varies between 1.3 and 2.3, CVEs being the main cause of death in these patients[3].

The causes leading to CVEs include atherosclerosis and macro/microvascular coronary artery disease; pericardial, myocardial, and vascular inflammation; heart valve disease; congestive heart failure; and pulmonary artery hypertension[4]. Accelerated atherosclerosis and atheromatous plaque rupture are related to vascular inflammation in patients with RA, adding disease-specific risk factors to the traditional risk factors like smoking, arterial hypertension, and dyslipidemia[5].

Traditionally, intima-media thickness (IMT) of the carotid artery has been used as an easy-access, low-cost measure to evaluate established vascular atheromatous disease. In recent times, 18F-Fluorodeoxyglucose Positron Emission Tomography (PET-FDG/TC) has emerged as an alternative to IMT for the evaluation of vascular wall inflammation, being both sensitive and specific[6]. Several studies have evaluated vascular inflammation in different diseases (psoriasis, chronic kidney disease, non-alcoholic fatty liver disease, and diabetes)[7], demonstrating inflammatory vascular disease by this method and showing its change across time. Uptake of 18F-FDG in the arterial walls is a common finding in patients with diseases

associated with vascular inflammation, and endothelial inflammation measured by PET-FDG/TC correlates with disease activity in RA[8]. This can be modified with pharmacologic interventions, as shown in a study evaluating patients with RA after starting triple therapy, where early changes in vascular inflammation could be seen after 4 weeks of treatment, and by week 12, a correlation was found between vascular inflammation and disease activity[9]. Some retrospective studies have demonstrated that 18F-FDG arterial uptake is associated with major CVEs[10].

The introduction of new drugs and the consolidation of the "treat-to-target" (T2T) strategy have drastically changed the evolution of RA and diminished associated mortality[11]. Janus Kinase (JAK) inhibitors, such as tofacitinib, have been proven effective in controlling disease activity in RA patients failing methotrexate and biologic treatments[12]. JAKs are involved in signal transduction in multiple cytokine pathways related to the inflammatory response[13], and the reduction of the inflammatory activity may lead to a reduction in arterial wall inflammation. However, recent data from the ORAL SURVEILLANCE study shows an elevated cardiovascular risk in certain populations of patients treated with tofacitinib as compared to those treated with tumor necrosis factor-alpha (TNF-alpha) inhibitors[14]. Data about cardiovascular safety made an impact on the FDA position statement on the use of JAK inhibitors as in the recently published EULAR guidelines[15], but clinical implications are being debated.

The aim of this study is to evaluate the endothelial vascular inflammation using PET-FDG/TC in patients with active RA initiating tofacitinib at baseline and after 12 weeks of treatment. As a secondary objective, to evaluate the frequency of carotid atheromatous plaque at baseline and at week 12.

MATERIALS AND METHODS

An observational, prospective, multicentric study was performed. Consecutive patients that were to start tofacitinib (5 mg BD or 11 mg QD) prescribed by their treating physician were included if they met the following criteria: RA fulfilling ACR/EULAR 2010 classification criteria15; ≥18 years old; moderate/high disease activity by Disease Activity Score 28- ($DAS28_{ESR}$) (>3.2)[16]; inadequate response to classic synthetic disease-modifying antirheumatic drugs (csDMARDs); and naïve of treatment with biologic disease-modifying antirheumatic drugs (bDMARDs). Exclusion criteria included: mayor cardiovascular events or risk factors (previous stroke, myocardial infarction, non-controlled congestive heart failure, diabetes); diagnosis of another inflammatory disease other than RA; prior history of chronic infection; chemotherapy or radiotherapy for cancer in the previous 5 years; patients with contraindications to the use of tofacitinib or PET/FDG-TC as judged by the investigator; and patients using statins or other hypolipemiant drugs. Tofacitinib was not provided by the investigators of this study.

The following data was assessed: sociodemographic data; RA duration since diagnosis; disease activity by $DAS28_{ESR}$ and Clinical Disease Activity Index (CDAI); function by Health Assessment Questionnaire (HAQ-A)[17]; treatments; prior cardiovascular events; smoking status (present/past/never); arterial hypertension; body mass index (BMI); and laboratory including blood cell count, ESR, C reactive protein (CRP), liver enzymes, cholesterol, HDL, LDL, and triglycerides.

Three visits were performed in this study in weeks 0, 4 and 12, according to Table 1. After the week 0 evaluation was completed, all patients started tofacitinib as prescribed by their treating physician.

PET-FDG/TC was performed at baseline (week 0) and at week 12 of tofacitinib treatment. Endothelial inflammation was assessed using maximum standardized uptake value (SUV) and maximum target-to-background ratio (TBR) in both carotid arteries and aorta (ascending, descending, and abdominal sections). A cut-off value of SUV≥1.6 was used as the definition of endothelial inflammation based on previous data9. Prior to performing the PET-FDG/CT, patients underwent a 5-hour fasting period. Blood glucose levels were confirmed to be ≤200 mg/dL before injection. A dose of 0.1 mCi/kg of body weight FDG was administered intravenously, followed by a waiting period of 60 to 75 minutes in a designated area. CT image acquisition was performed in the arterial phase, covering from the temporal region to the knees, followed by a

venous phase with the same anatomical range for attenuation correction. PET acquisition aligned with the venous range, with an acquisition time of 2 minutes per bed position, reduced to 1 minute per bed in the femoral region. The excretory phase spanned from the diaphragm dome to the pubis. The same observer has consistently interpreted all PET scans, which were conducted at the same center.

Carotid arteries doppler ultrasonography was performed at baseline and week 12 and intima-media thickness was measured. The frequency of patients with carotid artery plaque was established.

Descriptive statistics were performed. Continuous variables were expressed according to distribution as median (m) and interquartile range (IQR) or mean (x) and standard deviation (SD), and categorical variables were expressed as frequency and percentage. A comparison of initial characteristics between patients was performed using the Student's t test, Mann-Whitney's U test, ANOVA, Kruskal-Wallis, Chi^2, or Fisher's exact test according to the data analyzed. Pearson's test was used to correlate $DAS28^{ESR}$, CDAI, SUV_{max} and TBR_{max} and variation of SUV_{max} and TBR_{max} was analyzed using a linear model for repeated analysis. A p value <0.05 was considered significant. All analysis was performed using R.

The current investigation has undergone scrutiny and received endorsement from The Independent Ethics Committee for Clinical Pharmacology Trials of the Foundation for Pharmacological and Drug Studies, "Prof. Luis M. Zieher," which holds accreditation from the Central Ethics Committee in Research, CEI FEFyM (resolution I.G.J. No. 001062 dated December 19, 2001). The protocol is identified by the number CV-1001.

This research complies with the ethical tenets delineated in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, along with all relevant local statutes. The protocol has been meticulously examined to ascertain the safeguarding of participant rights, safety, and overall welfare. The independent ethics committee has scrutinized every facet of this protocol, encompassing participant recruitment, the informed consent process, and measures for data confidentiality, to guarantee adherence to the most rigorous ethical standards in clinical research.

Table 1: Study visits

	Week 0	Week 4	Week 12
DAS 28	X	X	X
HAQ	X		X
Apo A Apo B	X		X
Positron emission tomography	X		X
Carotid Doppler ultrasound	X		X
Physical exam	X	X	X
ESR and CRP	X	X	X
Cholesterol, HDL, LDL, and triglycerides	X	X	X

DAS28: Disease Activity Score; HAQ-A: Health Assessment Questionnaire-Argentinean version; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; HDL: high-density lipoprotein; LDL: light density lipoprotein; ApoA1: lipoproteins A1; ApoB: apolipoproteins.

RESULTS

Thirty patients were included in the study, 70% female, median age 57.5 (IQR 42-65) years old, with a median RA duration of 5 (IQR 2-12) years. Median DAS28ESR was 5.24 (IQR 4.6-6.1) and median CDAI 27.5 (IQR 20-34). Other characteristics are shown in Table 2.

At week 12 of tofacitinib treatment, patients showed, compared to baseline, a significant decrease in disease activity measured by DAS28ESR (5.21 vs 3.04; p<0.0001) and CDAI (26.6 vs 9; p<0.0001) and an improvement in function measured by HAQ (1.56 vs 1.1; p<0.0001). At week 12, a significant increase in total cholesterol (188 mg/dl vs. 207.5 mg/dl; p=0.004) and nominal increases in HDL, LDL, and triglycerides were found, with little impact on ApoA and ApoB (Table 3).

The 18F-FDG uptake in the five evaluated areas showed no significant difference between baseline and week 12 (Table 4), and all explored vascular areas showed a SUVmax over the prestipulated threshold defining inflammation at baseline. Doppler ultrasonography of carotidal arteries showed atheromatous plaques in 12 patients (40%), and this remained unchanged in week 12.

Table 2: Sociodemographic and clinical characteristics of the population.

Variables	n=30
Age (years), m (IQR)	57.5 (42-65)
Females, (%)	21 (70)
Comorbidities	
Arterial hypertension, n (%)	8 (26.7)
Smokers (currently), n (%)	2 (6.7)
Ex-smokers, n (%)	2 (6.7)
BMI, m (IQR)	25 (20-28)
Treatment	
Methotrexate, n (%)	14 (46.7)
Leflunomide, n (%)	1 (3.33)
Methotrexate + leflunomide, n (%)	15 (50)
Corticosteroids, n (%)	24 (80)
Prednisone doses (mg), m (IQR)	5 (5-10)

m: median; n: number; IQR: interquartile range; BMI: Body mass index

Table 3: Patients that received tofacitinib at baseline and at 6 months.

	Baseline visit	Week 12 visit	P value
DAS28 (ERS), m (IQR)	5.2 (4.6-6.1)	3 (2.4 - 3.5)	<0.001
CDAI, m (RIC)	27.5 (20-34)	9 (5-12)	<0.001
HAQ, m (RIC)	1.5 (1-2)	1.1 (0.75-1.4)	<0.001
Cholesterol (mg/dL), m (RIC)	188 (162-215)	207 (173-243)	0.004
HDL (mg/dL), m (RIC)	55 (44.5-64)	61 (49,5-68)	<0.001
LDL (mg/dL), m (RIC)	117.5 (97-141)	119 (85-146)	0.085
Triglycerides (mg/dL), m (RIC)	113 (95-151.5)	117 (86-158)	0.583
ApoA1, m (RIC)	170 (142-188)	172 (148-189)	0.935
ApoB, m (RIC)	100 (78-116)	98 (80-143)	0.157

ERS: erythrosedimentation; m: median; IQR: interquartile range; DAS28: Disease Activity Score; CDAI: Clinical Disease Activity Index; HAQ-A: Health Assessment Questionnaire-Argentinean versión; HDL: high-density lipoprotein; LDL: light density lipoprotein; ApoA1: lipoproteíns A1; ApoB: apolipoproteins.

Table 4: Vascular inflammation measured by PET-FDG/CT at baseline visit and week 12.

	SUVmax			TRBmax		
	Basal visit	Week 12	P value	Basal visit	Week 12	P value
Right common carotid artery, m (IQR)	1.9 (1.5-2.5)	1.9 (1.6-2.3)	0.327	0.8 (0.7-1.1)	0.9 (0.7-0.9)	1
Left common carotid artery, m (IQR)	1.9 (1.5-2.3)	1.8 (1.5-2.3)	1	0.8 (0.7-1.1)	0.9 (0.8-1.0)	0.571
Ascending aorta, m (IQR)	2.5 (2.1-3.0)	2.5 (2.3-2.9)	1	1.1 (1.0-1.3)	1.1 (1.1-1.3)	1
Descending aorta, m (IQR)	1.6 (1.4-1.9)	1.6 (1.5-1.8)	0.248	1.1 (0.9-1.2)	1.1 (1.0-1.3)	0.26
Abdominal aorta, m (IQR)	2.6 (2.2-2.8)	2.4 (2.12.80)	0.855	1.1 (1.0-1.2)	1.1 (0.9-1.2)	0.327

m: median; IQR: interquartile range; PET-FDG/CT: positron emission tomography with fluorodeoxyglucose uptake.

DISCUSSION

This study aimed to evaluate the effect of tofacitinib treatment on vascular inflammation measured by PET-FDG/TC. To our knowledge, this is the first study evaluating changes in vascular inflammation using this technique in patients initiating tofacitinib treatment.

In our patients, we found no change in vascular inflammation at week 12 of treatment. Haavisto et al.[9] showed a decrease in vascular inflammation after 4 weeks of triple csDMARD therapy in treatment-naive patients with RA. Interestingly, this difference in results is in spite of similar SUVmax values at baseline between the two studies.

The presence of vascular inflammation in patients requiring progression to advanced therapy is logical at the first visit because these patients have uncontrolled disease. However, we did not observe a decrease in vascular inflammation despite better control of disease activity.

In Solomon et al.[18], vascular inflammation measured by PET-FDG/TC was evaluated in patients randomly assigned to a TNF-alpha inhibitor vs. triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine). In this study, both groups improved their disease activity, but an association between articular improvement and vascular inflammation was not found. This finding is similar to the one from our study, and it may reinforce the idea that the mechanism behind vascular inflammation in RA is not limited only to the process of articular inflammation and has other variables not yet identified that fuel the elevation of cardiovascular risk in these patients.

Vascular inflammation measured by PET-FDG/TC was also evaluated by Bernelot Moens et al.[19] in patients with RA in clinical remission for at least 6 months. In this study, patients in remission who were currently on TNF-α inhibitor therapy or who had previously received a TNF-α inhibitor and discontinued it due to sustained remission were compared with matched control patients. Globally, vascular inflammation in RA patients in remission was comparable to that of control patients (aortic TBRmax 2.3±0.5 vs. 2.1±0.3; p=0.251). However, in the subanalysis, RA patients in remission currently receiving a TNF-α inhibitor showed higher vascular inflammation than patients in remission who no longer required such therapy despite similar disease control. This dissociation between adequate disease control and persistent vascular inflammation is consistent with our study's results.

The alterations in serum lipids found in our study are in line with those reported in previous studies[12], and it has been shown that the reduction in serologic inflammatory markers correlates with the increase in HDL and LDL in patients with RA treated with tofacitinib[20]. The exact mechanism behind this "lipid paradox" is still unknown, but it may be mediated by a lower accumulation of lipids in synoviocytes and macrophages due to the restitution of the function of the ABCA1 protein that is down-regulated during inflammation by IFNγ[21]. In the ENTRACTE trial, a phase 4 trial comparing the cardiovascular safety of tocilizumab vs. etanercept in RA[22], an elevation of serum lipids by IL-6 inhibition was found, but it didn't lead to any difference in cardiovascular risk during this study.

Chronic inflammation is the cornerstone of rheumatic disease pathogenesis, and it plays a key role in all the stages of atherosclerotic damage. The elevated incidence of cardiovascular events in these patients reduces their life expectancy compared to the general population. Despite the reduced cardiovascular mortality associated with the use of a T2T strategy, the role of tofacitinib in cardiovascular risk today remains obscure, and the lack of diagnostic algorithms for the early detection of cardiovascular disease in patients with rheumatic diseases is an ongoing unmet need[4]. Furthermore, the high cost and relatively low availability of PET-FDG/TC might make it difficult to make massive use of this technology in these patients.

In the ORAL SURVEILLANCE study[14], a higher cardiovascular risk was found in RA patients treated with tofacitinib compared to those treated with TNF inhibitors. It's interesting to note that in our study we did not find an increase or decrease in vascular inflammation measured by PET-FDG/TC in patients treated with tofacitinib. Several real-life studies have failed to prove the increase in cardiovascular risk of tofacitinib as compared to TNF inhibitors, so the exact role of tofacitinib in cardiovascular risk and the mechanisms behind it are currently still under evaluation.

A limitation of the current study is the short follow-up period and the limited number of included patients. However, this data may prove useful for further study of endothelial inflammatory processes that lead to the elevated cardiovascular mortality in patients with rheumatic diseases and the effect of the current therapeutics on it.

In conclusion, in this study, we found no change in vascular inflammation at week 12 of tofacitinib treatment, despite improvement in disease activity. A percentage of this patient group is likely to have atherosclerosis, which may complicate the evaluation of vascular inflammation. Additionally, limitations related

to sample size and the short duration of follow-up challenge the interpretation due to the lack of significant variation in vascular inflammation rates.

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