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PROSPECTIVE STUDY

TNF-α inhibitors and tocilizumab do not influence hepatic steatosis in patients with rheumatoid arthritis

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Abstract

AIM: To investigate the influence, if any, of tumor necrosis factor (TNF)-α inihibitors and Tocilizumab, on hepatic steatosis (HS) in rheumatoid arthritis (RA) patients in the light of the known role of TNF-α and interleukin-6, which are key-cytokines in the pathogenesis of RA, in inducing HS in general population.

METHODS: We retrospectively reviewed the clinical charts of 36 RA patients, out of whom 12 had been treated with Methotrexate (MTX), 12 with TNF inhibitors ± MTX and 12 with Tocilizumab ± MTX. The 3 subgroups of patients matched each other for sex, age, body mass index, metabolic syndrome (MS) and other risk factors for atherosclerosis. At baseline and after 12 mo each patient underwent an abdominal ultrasonography for the assessment of presence of HS and the evaluation of its grade.

RESULTS: No difference was detected either in the prevalence of HS or in that of its distinct grades between the 3 groups of patients at baseline. After 12 mo, the HS grade unchanged in 20 patients (7 subjects treated with MTX, 7 with TNF-α inhibitors ± MTX and 6 Tocilizumab ± MTX); increased in 12 patients (4 subjects treated with MTX, 4 TNF-α blockers ± MTX and 4 Tocilizumab ± MTX); decreased in 4 (1 treated with MTX, 1 with anti-TNF-α + MTX and 2 with TCZ ± MTX (P = 0.75). No correlation was found between getting remission or low disease activity and the course of either MS or HS.

CONCLUSION: We failed to detect any influence of MTX ± TNF-α inhibitors or Tocilizumab in reducing MS and HS. A prospective study is needed to clarify the topic.

Key words: Steatosis; Rheumatoid arthritis; Biological agents

Core tip: Tumor necrosis factor (TNF)-α and interleukin-6 are not only key-cytokines in the pathogenesis of rheumatoid arthritis (RA) but can also inducing hepatic steatosis (HS) in general population. RA patients treated with Methotrexate (MTX) or TNF-α inhibitors or Tocilizumab underwent an abdominal ultrasonography for the assessment of presence of HS and the evaluation of its grade. At baseline and after 12 mo no difference was detected either in the prevalence of HS or in that of its distinct grades between the patients treated with MTX or TNF-α inhibitors or Tocilizumab.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder, characterized by symmetrical synovitis ensuing in artricular destruction and disability and associated with a shorter life span, mainly due to cardiovascular disease[1,2].

The pathogenesis of accelerated atherosclerosis in RA has not been fully unraveled. Nevertheless, inflammation, prothrombotic state, insulin resistance and metabolic syndrome (MS) are all thought to play a role[3-5].

MS represents a clustering of specific cardiovascular disease risk factors including central abdominal obesity, arterial hypertension, fasting hyperglycemia, hypertriglyceridemia and low high density lipoprotein (HDL) levels[6]. It mainly depends on insulin resistance[6] and is associated with several obesity-related disorders including fatty liver disease evolving in some cases to fibrosis and cirrhosis[7].

Tumor necrosis factor (TNF)-α and interleukin-6 (IL-6), which play a definite role in the pathogenesis of RA[8], are also involved in inducing MS. Actually, TNF-α-promotes insulin resistance by decreasing tyrosine kynase activity of the insulin receptor and consequently reducing insulin activity[9]. Accordingly, blocking TNF-α in patients with MS has been reported to improve fasting glucose levels[9] and anti-TNF-α therapy in RA promotes insulin sensitivity, suggesting that TNF-α has an important role in inducing insulin resistance mediated by inflammation[10]. In addition, TNF-α inhibitors have been shown to influence surrogate markers of accelerated atherosclerosis such as intima-media thickness[11] and the incidence of cardiovascular events, at least in responsive patients[12]. In addition, IL-6 has been found to be associated with obesity-related insulin resistance, development of cardiovascular events and type 2 diabetes and hepatic steatosis, mainly its more severe form, *i.e.*, steatohepatitis[13,14]. Accordingly, anti-IL-6r therapy with Tocilizumab has also been reported to improve vascular function as assessed by pulse wave velocity[15].

At the best of our knowledge, no study has been so far devoted to investigate the influence of anti-TNF-α agents and Tocilizumab on hepatic steatosis (HS) in RA. This study was planned in order to have a preliminary view on the topic.

MATERIALS AND METHODS

For the purpose of the present study, we retrospectively reviewed the clinical charts of RA patients satisfying 1987 ACR criteria for the classification of RA[16], who had been admitted to the Rheumatology Unit of the Second University of Naples from January 1st to December 31st 2012. Among them, we selected those who had been followed for at least 12 mo, had undergone an abdominal ultrasound (US) at admission and after 1 year, had been treated with either Methotrexate (MTX) or anti-TNF-α agents ± MTX or Tocilizumab ± MTX and were matchable each other for sex, age, body mass index (BMI), MS and other risk factors for atherosclerosis. MS was ascertained according to World Health Organization (WHO)[17], *i.e.*, the patient had to present a fasting glucose level ⩾ 110 mg/dL plus at least 2 among HDL cholesterol < 40 mg/dL for women and < 35 mg/dL for men, serum tryglicerides ⩾ 150 mg/dL, BMI > 30 kg/m^2 and arterial blood pressure ⩾ 140/90 mmHg or use of antihypertensive drugs.

At baseline, each patient had been assessed for demographic characteristics, disease duration and autoantibody status. At baseline and, subsequently, every 3 mo, each patient had undergone a complete history, clinical and laboratory evaluation including tender and swollen joints count/28, Erythrosedimentation rate mm/h, C reactive protein (mg/dL), assessment of the Disease Activity Score 28 as a measure of disease activity[18], evaluation of Health Assessment Questionnaire[19] as a measure of functional disability, the list of concomitant drugs and comorbidity conditions.

At baseline (T0) and at 12 mo (T1) each patient underwent an abdominal US for the assessment of presence of HS and the evaluation of its grade. Liver echogenicity, indicative of HS, was evaluated by comparing it with that of kidney cortex and graded into 4 grade scale: Grade 0 (absent) = iso-echogenicity; Grade 1 (mild) = diffuse and homogeneous hyperechogenicity; Grade 2 (moderate) = attenuation of the ultrasound signal; Grade 3 (severe) = lack of diaphragm profile visualization[20].

Statistical analysis

Continous and Categorial variables were analyzed with Student's *t*-test and χ^2 test, respectively. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using InStat3 DATASET.1ISD software.

RESULTS

From January the 1st to December the 31st 2012, 281 RA patients were admitted to the Rheumatology Unit of the Second University of Naples and followed up for the subsequent 12 mo. Out of them, 85 were prescribed a new treatment: 38 with MTX, 47, who had been resulted to be non-responders or intolerant to traditional DMARDs, with either TNF-α blockers ± MTX; or with Tocilizumab ± MTX. Looking for matching for sex, age, BMI and other risk factors for atherosclerosis, we identified 36 RA patients out of whom 12 had been treated with MTX only, 12 with TNF inhibitors ± MTX and 12 with Tocilizumab ± MTX.

Table 1 lists the epidemiologic and clinical features of the 36 patients subdivided according to the three treatment arms assessed at baseline.

Table 1 Epidemiologic and clinical features of the 36 rheumatoid arthritis patients subdivided into 3 treatment arms *n* (%)

Features	MTX (*n* = 12)	Anti-TNF-α[1] ± MTX (*n* = 12)	Tocilizumab ± MTX (*n* = 12)	*P*
Age (mean ± SD), yr	56 ± 8	54.5 ± 9	58 ± 6	0.500
Sex (F/M)	11/1	11/1	11/1	1.000
Disease duration (yr, median, IQR)	5 (2-30)	11 (2-30)	13 (1-30)	0.030
DAS28 (median, IQR)	3.7 (1.5-6.5)	4.85 (3.5-6.1)	5.2 (2.4-6.2)	0.200
HAQ (median, IQR)	0.8 (0-1.875)	1.125 (0.125-2.875)	1.75 (0.375-2.7)	0.040
US steatosis (grade > 1)	7 (58)	5 (42)	7 (58)	0.900
MS	2 (17)	2 (17)	1 (8)	0.500
Fasting blood glucose ⩾ 110/mg per dL	2 (17)	2 (17)	1 (8)	0.500
BMI ⩾ 25	6 (50)	6 (50)	6 (50)	1.000
BMI ⩾ 30	3 (25)	2 (17)	1 (8)	0.500
HDL cholesterol < 40 mg/dL	2 (17)	1 (8)	0	0.300
Triglycerides > 150 mg/dL	0	3 (25)	1 (8)	0.100
Arterial hypertension	3 (25)	2 (17)	3 (25)	0.850
Corticosteroids ⩾ 5 mg/d	10 (83)	11 (92)	12 (100)	0.300
MTX use	12 (100)	4 (33)	5 (42)	0.001
MTX dosage (mean ± SD)	12.5 ± 3	15 ± 9	13 ± 3	0.009
Comorbidities[2]	4 (33)	3 (25)	6 (50)	0.400

[1]4 Etanercept; 8 Adalimumab; [2]7 autoimmune thyroiditis; 2 chronic obstructive pulmonary disease; 4 Cardiovascular disease. Data are numbers and percentages (inbrackets) except were otherwise specified. F/M: Female/male; DAS28: Disease Activity Score 28; HAQ: Health Assessment Questionnaire; MTX: Methotrexate; BMI: Body mass index; MS: Metabolic syndrome; TNF-α: Tumor necrosis factor-α; IQR: Interquartile range; US: Ultrasound; HDL: High density lipoprotein.

As planned, no difference was detected among the three groups in sex, age, BMI. In addition, no difference emerged in disease activity, steroids use, MTX dosage and prevalence of MS, or MS-related co-morbidities such as arterial hypertension or type 2 diabetes. Importantly, no difference was detected either in the prevalence of HS or in that of its distinct grades. Actually, at baseline 8/36 subjects [three tocilizumab (TCZ), two anti-TNF-α, three MTX] showed a mild HS (grade 1), 9/36 (four TCZ, two anti-TNF-α, three MTX) moderate HS (grade 2), 2/36 (1 anti-TNF-α, 1 MTX) severe HS (grade 3). However, patients treated with anti-TNF-α blockers or Tocilizumab had a longer disease duration ($P = 0.03$) than those treated with MTX.

At 12 mo, HS (grade > 1) was detected in ten MTX patients compared to seven at baseline; in eight TNF-α inhibitors with respect to five at baseline and in eight Tocilizumab with respect to seven at baseline. Moreover, the HS grade unchanged in 20 patients: seven subjects treated with MTX, seven TNF-α inhibitors and six Tocilizumab; increased in 12 patients: four subjects treated with MTX, four TNF-α blockers and 4 Tocilizumab; decreased in four: one subjects treated with MTX, one with anti-TNF-α and two with TCZ ($P = 0.75$).

No correlation was found between the state of remission or low disease activity and the course of either MS or HS.

DISCUSSION

We undertook the present retrospective study in order to assess the effect, if any, of MTX alone or in combination with either TNF inhibitors or Tocilizumab on HS in RA patients. We were moved to address this topic by a number of considerations: (1) RA is associated with increased cardiovascular morbidity and mortality, which is at least in part dependent from the occurrence of MS[2,5] in RA patients; (2) MS is associated with a higher incidence of HS[7]; (3) TNF and IL-6 are known to play a certain role in inducing HS in the general population[9,13,14]; (4) MTX and TNF-α inhibitors have been reported to reduce the cardiovascular burden in RA[21,22]; and (5) Tocilizumab is known to influence particular surrogate markers of accelerated atherosclerosis in RA[15].

First of all, we need to clarify that our study was not devoted to investigate the prevalence of MS and HS in RA because we did not investigate consecutive RA patients. Actually, we introduced a substantial bias by selecting patients in whom a baseline and 12 mo later hepatic US were available. Nevertheless, the registered prevalence of MS in our series (18%) is very close to that reported by other authors[23] in a larger number of patients. Moreover, that of HS is similar to that registered in 48 patients with psoriatic arthritis from our geographic area by Di Minno *et al*[24].

We assessed both MS and HS by validated methods. Indeed, according to WHO suggestions, we assessed the presence of MS by considering BMI, fasting levels of glucose, triglycerides as well as HDL cholesterol, and arterial pressure[17]. Moreover, US is considered a validated method to assess HS[20].

The discrepancy between the high incidence of HS and the relatively lower prevalence of MS might depend on the high incidence of HS reported in RA untreated patients by Rau *et al*[25]. These Authors investigated for liver histology 60 MTX-naïve patients and 40 MTX-treated patients and found no difference in either mesenchymal (Kupffer cell proliferation, portal tract infiltration) and parenchymal alterations (nuclear variability, ballooning, fatty infiltration) (72% *vs* 77% and 85% *vs* 89%).

As far as the objective of our study is concerned, we failed to detect any influence of MTX +/-TNF inhibitors

or Tocilizumab in reducing MS and HS. Actually, HS did not improve either in the whole series (four presenting a decreasing grade, 20 the same grade, 12 a greater grade) or in any of the three treatment arms (MTX = one presenting a decreasing grade, seven the same grade, four a greater grade; TNF-α inhibitors ± MTX = one presenting a decreasing grade,seven the same grade, four a greater grade; Tocilizumab ± MTX = two presenting a decreasing grade, six the same grade, four a greater grade).

Our study bears some limitations including the low number of investigated patients, the retrospective nature and a possible selection bias due to availability of hepatic US in a restricted number of patients. Therefore, since its rationale seems to be supported by a number of evidence, our conclusions must be challenged by a prospective, controlled study. In the meanwhile, the RA patient with HS should be carefully followed for the increased incidence of drug side effect and the possible evolution into the more severe form of HS, *i.e.*, nonalcoholic steatohepatitis, which shares similar inflammatory mechanisms involved in RA.

COMMENTS

Background

Tumor necrosis factor (TNF)-α and interleukin-6 (IL-6) are known to play a role in inducing hepatic steatosis (HS) in the general population, but are also the key-cytokines in the pathogenesis of rheumatoid arthritis (RA). At the best of people knowledge, no study has been so far devoted to investigate the influence of anti-TNF-α agents and Tocilizumab on HS in RA patients.

Research frontiers

The authors assessed both metabolic syndrome (MS) and HS by validated methods. Indeed, according to World Health Organization suggestions, they assessed the presence of MS by considering body mass index, fasting levels of glucose, triglyceridemia, high density lipoprotein cholesterol, and arterial pressure. Moreover, ultrasound is considered a validated method to assess HS.

Innovations and breakthroughs

Authors' study was not devoted to investigate the prevalence of MS and HS in RA because people did not investigate consecutive RA patients. This study has some limitations including the low number of patients investigated, the retrospective nature and a possible selection bias due to availability of hepatic US in a restricted number of patients. Since its rationale seem to be supported by a number of evidence, these conclusions must be challenged by a prospective controlled study.

Applications

At baseline and after 12 mo 36 RA patients treated with Methotrexate (MTX) or TNF-α inhibitors or Tocilizumab underwent an abdominal ultrasonography for the assessment of presence of HS and the evaluation of its grade. As far as the objective of this study is concerned, the authors failed to detect any influence of MTX +/-TNF inhibitors or Tocilizumab in reducing MS and HS.

Terminology

MS represents a clustering of specific cardiovascular disease risk factors including central abdominal obesity, arterial hypertension, fasting hyperglycemia, hypertriglyceridemia and low HDL levels. It mainly depends on insulin resistance and is associated with several obesity-related disorders including fatty liver disease evolving in some cases to fibrosis and cirrhosis. TNF-α promotes insulin resistance by decreasing tyrosine kynase activity of the insulin receptor and consequently reducing insulin activity. IL-6 has been found to be associated with obesity-related insulin resistance, development of cardiovascular events and type 2 diabetes and hepatic steatosis, mainly its more severe form, *i.e.*, steatohepatitis. Liver echogenicity, indicative of HS, was evaluated by comparing it with that of kidney cortex and graduated into 4 grade scale: Grade 0 (absent) = isoechogenicity; Grade 1 (mild) = diffuse and homogeneous hyperechogenicity; Grade 2 (moderate) = attenuation of the ultrasound signal; Grade 3 (severe) = lack of diaphragm profile visualization.

Peer review

The article describes an interesting study.

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

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Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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