Effects of CTLA-4Ig compared to TNFi on lipid profile: results from an observational multi-centre rheumatoid arthritis cohort of the "Cardiovascular Obesity and Rheumatic DISease (CORDIS)" Study Group of Italian Society of Rheumatology (SIR).

Fabiola Atzeni, etc…

[1] Rheumatology Unit, Department of Experimental and Internal Medicine, University of Messina, Messina, Italy

 # Corresponding author:

Fabiola Atzeni, MD, PhD

Full Professor of Rheumatology, Head of Rheumatology Unit,

University of Messina,Via C. Valeria 1,

98100 Messina, Italy

Tel: +39 0902009; Fax: +39 0902000

E-mail: atzenifabiola@hotmail.com

Running title: Effects of CTLA-4Ig versus TNFi on lipid profile

Brief paper or letter to the Editor

Manuscript content: abstract (…250 words), 1500 words, 15 references, 1 figure

ABSTRACT

Objective: to evaluate the impact of selective T-cell costimulator inhibitor (CTLA-4Ig) compared to tumor necrosis factor inhibitors (TNFi) on cardiovascular (CV) clinical and laboratory outcomes in patients with rheumatoid arthritis (RA).

Methods: We performed a prospective study of RA patients included in the "Cardiovascular Obesity and Rheumatic DISease (CORDIS)" Study Group database collecting demographic, clinical, and laboratory data of those starting a CTLA-4Ig or TNFi at baseline, 6- and 12-month follow-up.

Results: Of the 206 RA patients without previous CV events enrolled in the study, 64 received a CTLA-4Ig and 142 a TNFi. The two groups did not differ in age, gender, or smoking habits, and the prevalence of hypertension, diabetes, and metabolic syndrome was similar. Over a follow-up period of 12 months, although no significant differences were found in the disease activity course, we observed that LDL cholesterol levels slightly decreased only in the CTLA-4Ig treated patients.

Conclusions: Patients treated with CTLA-4Ig and TNFi did not differ in disease activity response and traditional CV risk factors. However, CTL-A-4Ig treatment is associated with a favorable change of lipid profile at 12-month follow-up.

Key words: cardiovascular risk factors; CTLA-4Ig; TNFi.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease characterized by the involvement of synovial joints associated with several extra-articular manifestations and comorbidities, mainly regarding the cardiovascular (CV) system [1]. Specifically, research demonstrated increased morbidity and mortality from CV events in RA patients [2]. A meta-analysis including 14 controlled observational studies indicated that patients with RA have a 48% higher risk of incident CV events compared to the general population due to an increased risk of myocardial infarction (68%) and cerebrovascular accidents (41%) [3]. The excess CV risk in RA is related to early, progressive, inflammatory atherosclerosis in conjunction with endothelial dysfunction [4]. As the development of CV disease is a chronic inflammatory process involving the same cytokines and cells implicated in the RA pathogenesis [5], the disease-modifying anti-rheumatic drugs (DMARDs) used to treat the joint inflammation may help restrain atherosclerosis [6].

In particular, drugs acting by inhibiting the pro-inflammatory cytokine tumor necrosis factor (TNF), which plays a central role in RA development, atherosclerotic plaque formation and growth, are potentially effective [6]. A meta-analysis has shown that both TNFi and methotrexate (MTX) are associated with a decreased risk of all CV events in RA patients (relative risk 0.72; 95% CI 0.57–0.91; P = 0.007 and 0.70; 95% CI 0.54–0.90; P = 0.005, respectively) [7]. In contrast to the well-investigated effects of conventional, targeted synthetic and biological (b) DMARDs in controlling joint inflammation and disease progression, the potential anti-atherosclerotic action of specific therapies is still unclear. The cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)Ig is a novel, first-in-class drug exerting its effect by modulating a co-stimulatory CD80/CD86-CD28 signal necessary for T-cell activation [6]. It is a recombinant protein composed of the extracellular domain of the CTLA 4 fused with immunoglobulin G domains. Treatment with CTLA-4Ig seems to improve the lipid profile [9] and whole-body insulin sensitivity [10], suggesting its potential role in reducing CV risk in RA patients with comorbid diabetes [11,12].

The aim of this observational, multicenter study was to compare the effects of CTLA-4Ig versus those of TNFi on CV risk factors in a cohort of RA patients included in the database of the "Cardiovascular Obesity and Rheumatic DISease (CORDIS)" Study Group of the Italian Society of Rheumatology, a collaborative initiative to improve knowledge on the interrelationship between rheumatic, metabolic, and CV diseases [12].

Methods

Data of consecutive patients fulfilling the 2010 American College of Rheumatology (ACR)/EULAR classification criteria for RA [13] starting treatment with a CTLA-4Ig or a TNFi were recorded at baseline and every six months for one year.

The following demographic and clinical data were collected at enrollment: age, sex, smoking status (current, former, never), body mass index (BMI), systolic and diastolic blood pressure values, fasting glucose, lipid levels (total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG)). Moreover, the presence of hyperlipidemia, diabetes mellitus (DM), and hypertension was evaluated according to the following criteria. Hyperlipidemia was defined as the use of lipid-lowering medications and/or a TC level of ≥ 200 mg/dl (i.e., 5.7 mmol/L). Hypertension was defined as either a former medical history of hypertension or the current use of blood pressure-lowering drugs. Diabetes was defined based on previous medical history and/or the use of oral hypoglycemic drugs or insulin. All CV events (such as myocardial infarction, unstable angina, ictus and previous coronary revascularization procedures) were retrieved and all subjects with previous CV events were excluded from the analysis.

Disease activity scored by DAS28 and CDAI was recorded. RA serologic status assessment included rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA). Finally, ongoing anti-hypertensive, anti-diabetic, and lipid-lowering therapies were recorded, as well as anti-rheumatic drugs, including conventional synthetic (cs) DMARDs, and corticosteroids (mean weekly dose since diagnosis and the current daily dose of prednisone or equivalent). The study, conforming to the ethical

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guidelines of the Declaration of Helsinki, was approved by the local Ethical Committee as part of the GISEA Registry protocol (approval number DG-624/2012). Written informed consent was obtained from all patients at the start of the observational period.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, whereas categorical ones were expressed as numbers and percentages (n,%). Differences between the two groups were evaluated using the paired t-test in continuous variables and the Fisher's exact test in categorical data. A mixed effects model was used to describe the change in lipid profile over time. Lipid values were included as unstructured data in the model, with a cubic spline with three knots to account for non-linear change over time. Models were adjusted for age and gender. Confidence intervals were calculated using robust standard errors. A p-value < 0.05 was considered statistically significant. The software Stata 17 was used for all analyses.

Results

Overall, 206 RA patients without prior CV events were enrolled in this multicenter study. Of them, 64 were taking CTLA-4Ig and 142 a TNFi. A comparison between demographic, clinical and laboratory of the two groups at inclusion is reported in Table I. The two groups did not differ in age, gender, smoking habits, and RA diagnosis (non è chiaro) (disease duration? Erosive disease? Disease activity?) according to the different diagnostic criteria. The prevalence of hypertension, DM and metabolic syndrome was similar in both groups while the seropositivity was slightly higher in CTLA-4Ig group than in this taking TNFi (lo toglierei da qui visto che viene specificato dopo). Prevalence of RF and ACPA positivity was significantly higher in the CTLA-4Ig than in TNFi group (p < 0.001). Similarly, frequency of extra-articular manifestations was higher in CTLA-4Ig than in TNFi group (p < 0.001).

During treatment, all patients presented a significant improvement in disease activity (riportiamo DAS28 e CDAI) and EULAR response (se abbiamo il dato potremmo riportarlo). Stratifying patients

Commentato [MP3]: Consiglio di specificare quale % per ogni TNFi

Commentato [MP4]: concordo

according to the bDMARD treatment, no statistically significant differences were found in disease activity between patients treated with CTLA-4Ig or TNFi at any time point follow-up (p?).

Over a follow-up period of 12 months, LDL cholesterol levels slightly decreased in the CTLA-4Ig group in comparison tothe TNFi group (é significativo?) and the effect was particularly evident after the sixth month (Figure 1). No significant difference was observed in the other lipid parameters . **(Figure 1)**. Bisognerebbe focalizzare maggiormente l'attenzione su questo punto (infatti è l'unico rilevante)

Commentato [MP5]: è necessario esprimere dati quantitative, effect size e p value

Discussion

Recent lines of evidence support the favorable effects of cs and bDMARD therapy in reducing CV risk in RA by effective control of systemic inflammation and disease activity [14]. In this setting, by blocking different cytokines involved in the inflammatory response underlying RA pathogenesis, the beneficial CV profile of each drug may be different according to the specific mechanism. However, few studies performed a head-to-head comparison of the effect of different bDMARDs in improving or reducing CV risk in RA patients. In this study involving a cohort of RA patients starting two different biologic therapies, CTLA-4Ig use was associated with a slightly reduction of LDL-cholesterol levels at twelve months of treatment in comparison to TNFi use and the effect was particularly evident after the sixth month. Of note, at inclusion, prevalence of traditional CV risk factors such as hypertension, DM, hyperlipidemia and metabolic syndrome, did not differ in the two groups. . . Data on the lipid effects of CTLA4-Ig are relatively scares. In previous studies [8?], CTLA-4Ig produced an increase in TC, TG, and LDL-cholesterol, even not statistically significant, and a significant favorable increase in HDL-colesterol at six months in RA patients with long-standing disease [15]. Of note, though low HDL-C is a recognized marker of increased CV risk, the beneficial effect of raising HDL-cholesterol is discussed [16]. The blockade of costimulation and activation of cytotoxic T lym-

phocytes with consequent abrogation of inflammatory cytokine cascade, a specific and unique mechanism of action of CTLA-4Ig, may account for the beneficial effects of CTLA-4Ig in comparison to TNFi on lipid profile. Moreover, although the effects of CTLA-4Ig on several CV risk factors such as metabolic syndromeseem to be rather neutral in our cohort, thedrug has been demonstrated to improve insuline sensitivity and reduce CV disease risk in RA patients with DM in comparison to TNFi, thus reinforcing a possible drug-specific effect beyond the reduction of disease-related inflammation [9, 10, 15]. .

We aknowledege the present study has some limitations. First of all, this is the analysis of a limited population. Moreover, being a real-life setting study, we cannot exclude some missing data about disease features and its clinical management. Finally, residual confounding factors, such as diet adherence and physical activity, have not been considered in interpreting the results. However, the results of the present study provide a picture of a real-life population representative of different Italian settings. As the lipid profile has a central role in the development of CV diseases, elucidating the peculiar effects of each anti-rheumatic drugs in modulating lipoprotein levels and functions represents a central objective for a personalized treatment approach. However, though these lipid changes may reflect the CTLA-4Ig potential anti-atherogenic effect, the CV impact of these changes remains to be clarified.

Table 1. Demographic and clinical characteristics of patients

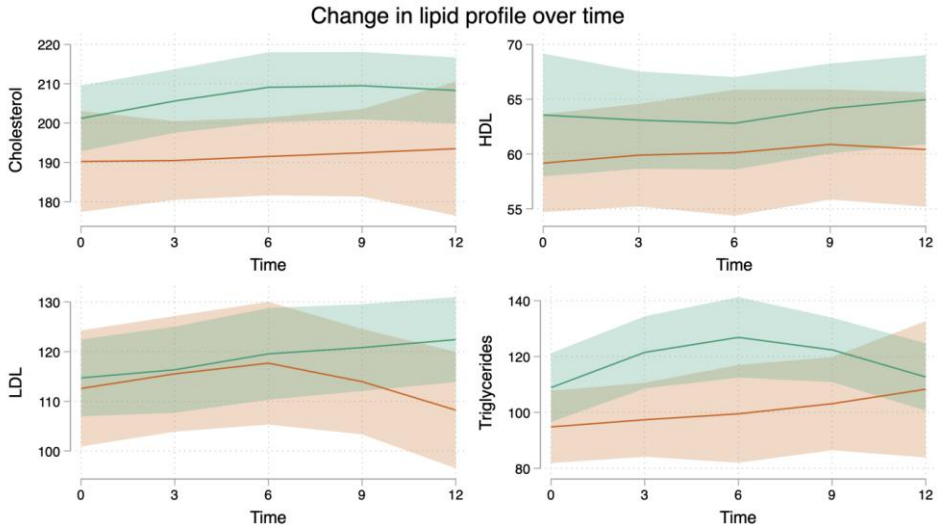
	Total	**CTLA-4Ig**	**TNFi**	**p-value**
	N=206	N=64	N=142	
AGE years – mean (SD)	59 (52.65)	60 (53.69)	59 (52.64)	0.23
GENDER				0.39

Female, n (%)	177 (85.9%)	53 (82.8%)	124 (87.3%)	
Male, n (%)	29 (14.1%)	11 (17.2%)	18 (12.7%)	
ETHNICITY				0.56
Caucasian, n (%)	204 (99.0%)	63 (98.4%)	141 (99.3%)	
Other, n (%)	2 (1.0%)	1 (1.6%)	1 (0.7%)	
SMOKER				0.54
No, n (%)	150 (74.6%)	46 (71.9%)	104 (75.9%)	
RHEUMATOID FACTOR				<0.001
No, n (%)	61 (29.8%)	8 (12.5%)	53 (37.6%)	
Yes, n (%)	144 (70.2%)	56 (87.5%)	88 (62.4%)	
ANTI-CITRULLINATED PROTEIN ANTIBODIES (ACPA)				<0.001
No, n (%)	66 (32.2%)	7 (10.9%)	59 (41.8%)	
Yes, n (%)	139 (67.8%)	57 (89.1%)	82 (58.2%)	
Methotexate users, n (%)				
Corticosteroid users, n(%)				
EXTRA-ARTICULAR MANIFESTATIONS				<0.001
No, n (%)	133 (64.6%)	28 (43.8%)	105 (73.9%)	
Yes, n (%)	73 (35.4%)	36 (56.2%)	37 (26.1%)	
DISEASE ACTIVITY (DAS28 or CDAI)				
Baseline / 6 months / 12 months				
METABOLIC SYNDROME_				0.79
No, n (%)	185 (94.4%)	60 (93.8%)	125 (94.7%)	
Yes, n (%)	11 (5.6%)	4 (6.2%)	7 (5.3%)	

Commentato [FC6]: Riporterei qui il dato sull'attività di malattia agli stessi tempi delle valutazioni dell'assetto lipidico.

DIABETES MELLITUS				0.25
No, n (%)	180 (90.9%)	56 (87.5%)	124 (92.5%)	
Yes, n (%)	18 (9.1%)	8 (12.5%)	10 (7.5%)	
HYPERTENSION				0.97
No, n (%)	111 (56.1%)	36 (56.2%)	75 (56.0%)	
Yes, n (%)	87 (43.9%)	28 (43.8%)	59 (44.0%)	
DYSLIPIDEMIA				0.10
No, n (%)	187 (94.4%)	58 (90.6%)	129 (96.3%)	
Yes, n (%)	11 (5.6%)	6 (9.4%)	5 (3.7%)	

Figure 1. Change in lipid profile over 12-month follow-up



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