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Lipoprotein(A) Concentrations In Rheumatoid Arthritis On Biologic Therapy: Results From The Cardiovascular In Rheumatology [Carma] Study Project

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**TITLE**: **LIPOPROTEIN(a) CONCENTRATIONS IN RHEUMATOID ARTHRITIS ON BIOLOGIC THERAPY: RESULTS FROM THE CARDIOVASCULAR IN RHEUMATOLOGY [CARMA] STUDY PROJECT.**

**RUNNING TITLE: BIOLOGIC THERAPY AND LIPOPROTEIN (A) IN RHEUMATOID ARTHRITIS**

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**ABSTRACT**

**Background:** Plasma concentrations of lipoprotein (a) [Lp(a)], a lipoprotein with atherogenic and thrombogenic properties, have a strong genetic basis, although high concentrations of Lp(a) have also been reported in the context of inflammation, as in rheumatoid arthritis (RA). Few studies evaluate the impact of biologic therapies (BT) on Lp(a) in RA, taking into account that with these new therapies a better control of inflammation is achieved.

**Objective**: Evaluate the plasma concentrations of Lp(a) in Spanish RA patients on BT attending rheumatology outpatient clinics.

**Methods:** Baseline analysis of the CARMA project, a 10-year prospective study evaluating the risk of cardiovascular events in RA and other forms of inflammatory arthritis. RA patients were classified according to treatment: no biologic, anti-tumor necrosis factor, anti-IL-6 receptor tocilizumab (TCZ), and other biologic (rituximab or abatacept). A model of linear multivariate regression was built in which the dependent variable was Lp(a) concentration and the explanatory variable was BT. The model was adjusted for confounding factors.

**Results**: Seven hundred and seventy-five RA patients were analyzed. Plasma concentrations of total cholesterol and triglyceride were significantly higher in TCZ-treated patients. Nevertheless, no significant difference in the atherogenic index between TCZ-treated patients and patients without BT was found. After adjusting for confounding factors, patients with BT had lower concentrations of Lp(a) than those without BT; however, only TCZ-treated patients achieved statistically significant differences (β: -0.303, 95% CI: -0.558 to -0.047; p=0.02).

**Conclusions**: RA patients treated with tocilizumab show lower plasma concentrations of Lp(a) compared to patients without BT.

**KEYWORDS**

Rheumatoid arthritis, cardiovascular disease, lipoprotein(a), biologics, tocilizumab.

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## INTRODUCTION

Beyond the quantitative and qualitative alterations in lipid metabolism reported in patients with rheumatoid arthritis (RA) related to inflammation, nonconventional atherogenic risk factors may also play a role in the increased cardiovascular (CV) risk of RA patients (1). In this sense, high levels of lipoprotein(a) [Lp(a)] have been observed in RA and other types of inflammatory arthritis (2, 3).

Serum concentrations of Lp(a), which has atherogenic and thrombogenic properties and is a lipoprotein regarded as an independent CV risk factor, are higher in patients with coronary artery disease (4). Lp(a) is structurally similar to the low-density lipoprotein cholesterol (c-LDL) molecule which, in addition to apolipoprotein B100 (apoB100), has another protein, the apolipoprotein (a) [apo(a)]. This apolipoprotein gives Lp(a) more atherogenic properties, based mostly on its size, and is genetically determined (5). The size heterogeneity of apo(a) is related to the variable number of copies of one of the protein domains, the Kringle IV type 2, and it has an inverse relationship with the density and the plasma concentration of Lp(a). Individuals with small apo(a) are those with the highest Lp(a) concentrations and increased cardiovascular risk (6). On the other hand, although plasma concentrations of Lp(a) have a strong genetic basis, as mentioned above, high concentrations of Lp(a) have also been reported in the context of inflammation.

Lp(a) seems to act as an acute-phase reactant. However, unlike traditional lipid metabolism, which is effectively modulated by treatment of the disease (2, 7), the effects of therapy on metabolism of Lp(a) in patients with RA remain unclear. This may be explained in part by the fact that genetic factors have a large impact on the variation of Lp(a) levels (8).

Better control of inflammation and disease activity in patients with RA has been achieved by the use of biologic therapies. However, there have been few studies that evaluate the impact of these new therapies on Lp(a) in RA (9, 10). This aspect is of particular interest because it has been observed that Lp(a) levels are higher in individuals with elevated interleukin-6 (IL-6) serum concentrations, as this proinflammatory cytokine increases the transcriptional activity of the apo(a) gene *LPA* (11).

Taking into account all of these considerations, the purpose of the present study was to evaluate the plasma concentrations of Lp(a) in Spanish patients with RA on biologic therapy attending Rheumatology outpatient clinics. These patients were enrolled in the CARdiovascular in rheuMAtology (CARMA), a 10-year prospective cohort study designed to determine the cardiovascular mortality risk in patients with chronic inflammatory rheumatic diseases, including those with RA.

## MATERIAL AND METHODS

### *Study design*

Cross-sectional analysis from the baseline visit of a 10-year prospective follow-up study CARMA. In this study, a cohort of patients with chronic inflammatory rheumatic diseases, including those with RA, were compared with another non-inflammatory cohort (12).

### *Patient recruitment*

Patients diagnosed with RA at sixty-seven Rheumatology Units selected from Spanish National Health System hospitals participated in the study. The participant Rheumatology Units were randomly selected after a probabilistic cluster sampling from the database of the Spanish Society of Rheumatology (SER). Inclusion criteria for the

recruitment period (July 2010 to January 2012) were as follows: patients diagnosed with RA according to the 1987 American College of Rheumatology classification criteria (13), aged 18 years or older, and signed informed consent by the patient. Information on the sample size of the project and baseline characteristics of the population were described by Castañeda et al (12). This study was performed following the principles outlined in the Helsinki Declaration and the study protocol was approved by the Ethics Committee for Clinical Research of Galicia, Spain.

***Variables and operative definitions***

Lp(a) plasma concentrations were considered the primary endpoint. All biochemistry determinations were made after an overnight fast and they were analyzed according to the methodology and reproducibility level of each participant institution.

The cohort with RA was evaluated following international protocols, including standardized definitions and validated questionnaires. All patients included in this study were continuously and systematically evaluated on-line and, to verify the quality of the information, *in situ* data monitoring was performed in 15% of randomly selected patients.

Treatment of RA, as an explanatory variable, was classified into four categories: no biologic therapy, anti-tumor necrosis factor (TNF) therapy, treatment with tocilizumab (TCZ), and other biological therapies (rituximab or abatacept).

Other variables analyzed were: (1) obesity (body mass index $\geq$ 30 kg/m2) and main physical activity during working hours (low activity: sitting most of the time; moderate activity: standing most of the time and with little movement or effort; intense activity: walking most of the time or performing tasks that require high physical activity); (2) traditional (classic) CV risk factors (hypertension, dyslipidemia, obesity, smoking, diabetes and family history of ischemic heart disease); (3) parameters of inflammation

and disease activity: rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (ACPA), erythrocyte sedimentation rate (ESR) (mm/1$^{st}$ hour), C-reactive protein (CRP) (mg/L), disease activity score including 28 joints and erythrocyte sedimentation rate (DAS28-ESR), health assessment questionnaire (HAQ (0–3)); (4) lipid and lipoprotein profiles: total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), apolipoprotein AI (apo AI), apolipoprotein B (apo B) and Lp(a), and (5) potential confounding factors such as the presence of erosions, duration of disease, atherogenic index (TC/HDL-c) and therapies. Hyperlipoproteinemia(a) was defined by a serum Lp(a) concentration > 50mg/dL.

***Statistical analysis***

Variables were described according to their typology and distribution. Categorical variables were described using frequencies and percentages. Differences between groups were compared using chi-squared tests. Continuous variables that followed a normal distribution were described using the mean and standard deviation (SD) and the differences between groups were assessed using ANOVA tests. Non-normally distributed variables were described with the median and interquartile range (IQR) and differences between groups were assessed with the Kruskal-Wallis non-parametric test. In all of the analyses a p-value $\leq 0.05$ was considered statistically significant.

Given the asymmetric nature of the outcome variable (Lp(a)), a logarithmic transformation was performed and the model was adjusted using multivariate linear regression. To reduce variability in the methods of measurement of Lp(a) across the participating hospitals, mixed linear multivariate regression models were constructed with robust variance estimators using the hospital as a cluster for variable estimation. The selection of adjusted variables in the multivariate model was based on clinical judgment and those with a p-value <0.20 in the bivariate analysis. Multicollinearity

among independent variables was also explored to build the model. In the model of linear multivariate regression, the explanatory variable (biologic therapy) was adjusted for confounding factors.

Data management and statistical analysis were centralized at the Research Unit of the SER following a pre-established analysis plan. All the analyses were performed using the SPSS 21.0 statistical program and Stata 13.1 (4905 Lakeway Drive. College Station, Texas 77845, USA).

**RESULTS**

Information on Lp(a) was available in 441 of the 775 (56.9%) patients with RA included in the CARMA study project. No baseline differences were observed between patients in whom Lp(a) was analyzed or not. The main demographic, clinical and laboratory features of the CARMA RA cohort are summarized in **Table 1**. Patients undergoing biologic therapy had longer disease duration. Erosive arthritis was more commonly observed in patients treated with anti-TNF. Patients on TCZ therapy were more commonly women and younger. Hypercholesterolemia and statin therapy were more commonly observed in TCZ-treated patients. TCZ-treated patients had lower disease activity as measured by DAS28 (2.71±1.41; p=0.01), but poorer scores on HAQ (1.3; IQR 0.6-1.6; p<0.001). The disease-modifying antirheumatic drugs (DMARD) prescription rate was lower in TCZ-treated patients (73.3%; p=0.005) than in those treated with other biologic therapies or not treated with biologic agents.

**Table 1. Sociodemographic and clinical characteristics of patients with rheumatoid arthritis stratified by type of therapy.**



| Variables | Total (n=775) | Non biological therapy (n=462) | Anti-TNF therapy (n=236) | Tocilizumab (n=30) | Other biologic therapies (n=47) | *p-value* |
|---|---|---|---|---|---|---|
| Age, years, mean ± SD | 45.8 ± 13.4 | 47.89 ± 13.66 | 43.03 ± 12.43 | 40.67 ± 12.73 | 42.85 ± 11.82 | <0.001 |
| Sex, female, n (%) | 581 (74.97) | 345 (74.68) | 179 (75.85) | 26 (86.67) | 31(65.96) | 0.227 |
| Educational level, n (%) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Elementary | 529 (68.97) | 319 (70.11) | 156 (66.38) | 19 (63.33) | 35 (74.47) | 0.23 |
| University / secondary | 238 (31.03) | 136 (29.89) | 79 (33.62) | 11 (36.67) | 12 (25.53) | |
| Main activity, n (%) | | | | | | |
| Sedentary | 236 (35.01) | 125 (31.65) | 84 (38.71) | 12 (48) | 15 (40.54) | 0.34 |
| Moderate | 290 (43.03) | 179 (45.32) | 86 (39.63) | 11 (44) | 14 (37.84) | |
| Active with displacement | 148 (21.96) | 91 (23.04) | 47 (21.66) | 2 (8) | 8 (21.62) | |
| BMI, kg/m$^2$, mean ± SD | 26.89 ± 4.82 | 26.83 ± 4.64 | 26.87 ± 5.12 | 27.42 ± 4.97 | 27.29 ± 5.03 | 0.85 |
| Obesity (BMI > 30), n (%) | 180 (23.23) | 101 (21.86) | 56 (23.73) | 8 (26.67) | 15 (31.91) | 0.46 |
| Smoking, status, n (%) | | | | | | |
| Current smokers | 189 (24.39) | 110 (23.81) | 57 (24.15) | 10 (33.33) | 12 (25.53) | 0.70 |
| Past smokers | 202 (26.06) | 122 (26.41) | 58 (24.58) | 6 (20) | 16 (34.04) | |
| Never smokers | 384 (49.55) | 230 (49.78) | 121 (51.27) | 14 (46.67) | 19 (40.43) | |
| Disease duration, years, mean ± SD | 10.23 ± 8.94 | 8.88 ± 8.80 | 12.47 ± 8.98 | 12.57 ± 8.59 | 10.72 ± 8.07 | <0.001 |
| DAS28 ESR, mean ± SD | 3.19 ± 1.25 | 3.13 ± 1.24 | 3.30 ± 1.19 | 2.71 ± 1.41 | 3.57 ± 1.38 | 0.01 |
| HAQ (0-3), median [p25-p75] | 0.5 [0.1-1.1] | 0.5 [0.12-1.0] | 0.7 [0.1-1.4] | 1.3 [0.6-1.6] | 0.75 [0.25-1.25] | <0.001 |
| ESR, mm/1$^{st}$ h, median [p25-p75] | 17 [9-29] | 17 [9-31] | 17 [9-28] | 6 [3-19] | 19 [9-29] | <0.001 |
| CRP (mg/L), median [p25-p75] | 3.0 [1.2-6.4] | 3.95 [1.5-7] | 2.1 [1.1-5.3] | 0.4 [0.2-1.1] | 3.2 [1.7-18.4] | <0.001 |
| Tender joint count (out of 28), median [p25-p75] | 1 [0-3] | 1 [0-3] | 1 [0-4] | 1.5 [0-4] | 3 [0-6] | 0.02 |
| Swollen joint count (out of 28), median [p25-p75] | 0 [0-2] | 0 [0-2] | 0 [0-2] | 1 [0-3] | 1 [0-3] | 0.36 |
| RF positive, n (%) | 594 (76.65) | 341 (73.81) | 190 (80.51) | 24 (80) | 39 (82.98) | 0.15 |
| ACPA positive, n (%) | 463 (59.74) | 267 (57.79) | 146 (61.86) | 19 (63.33) | 31 (65.96) | 0.55 |
| Erosive Arthritis, n (%) | 352 (45.42) | 170 (36.8) | 149 (63.14) | 13 (43.33) | 20 (42.55) | <0.001 |
| Cardiovascular disease, n (%) | 81 (10.5) | 49 (10.61) | 25 (10.59) | 1 (3.33) | 6 (12.77) | 0.591 |
| Diabetes, n (%) | 59 (7.61) | 39 (8.44) | 18 (7.63) | 0 (0) | 2 (4.26) | 0.30 |
| Hypertension, n (%) | 236 (30.45) | 138 (29.87) | 77 (32.63) | 11 (36.67) | 10 (21.28) | 0.39 |
| Hypercholesterolemia, n (%) | 238 (30.71) | 131 (28.35) | 74 (31.36) | 19 (63.33) | 14 (29.79) | 0.001 |
| Family history of IHD, n (%) | 96 (12.44) | 55 (11.98) | 34 (14.41) | 3 (10.00) | 4 (8.51) | 0.62 |
| DMARD, n (%) | 674 (86.97) | 416 (90.04) | 199 (84.32) | 22 (73.33) | 37 (78.72) | 0.005 |
| Glucocorticoids, n (%) | 357 (46.06) | 217 (46.97) | 97 (41.1) | 14 (46.67) | 29 (61.7) | 0.07 |
| NSAIDS, n (%) | 309 (39.87) | 179 (38.74) | 94 (39.83) | 16 (53.33) | 20 (42.55) | 0.45 |
| ACE inhibitors, n (%) | 76 (9.81) | 52 (11.26) | 20 (8.47) | 2 (6.67) | 2 (4.26) | 0.31 |
| ARBs, n (%) | 59 (7.61) | 32 (6.93) | 20 (8.47) | 4 (13.33) | 3 (6.38) | 0.56 |
| Statins, n (%) | 161 (20.77) | 91 (19.7) | 49 (20.76) | 14 (46.67) | 7 (14.89) | 0.004 |
| Beta blockers, n (%) | 50 (6.45) | 27 (5.84) | 18 (7.63) | 3 (10) | 2 (4.26) | 0.61 |
| Calcium antagonists, n (%) | 39 (5.03) | 22 (4.76) | 15 (6.36) | 2 (6.67) | 0 (0) | 0.31 |

TNF: tumor necrosis factor; SD: standard deviation; BMI: body mass index; RF: rheumatoid factor; ACPA: anti-cyclic citrullinated peptide antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28-ESR: Disease Activity Score using 28 swollen or tender joint count and ESR; IHD: ischemic heart disease; DMARD: disease-modifying antirheumatic drugs; HAQ (0-3): Health Assessment Questionnaire; NSAID: non-steroidal anti-inflammatory drugs; ACE: angiotensin converting enzyme; ARBs: angiotensin II receptor blockers

Serum lipids, lipoprotein and apolipoprotein values are shown in **Table 2**. Total cholesterol and TG were significantly higher in patients treated with TCZ than in the rest of patients with RA. However, no significant differences in the atherogenic index

were observed. By contrast, TCZ-treated patients exhibited statistically significant lower plasma concentrations of Lp(a) than the rest of RA patients included in the other groups. Of note, only a small percentage of TCZ-treated patients had hyperlipoproteinemia(a) **(Table 2)**. No other significant differences were found among groups.

**Table 2. Lipid and lipoprotein profiles of patients with rheumatoid arthritis stratified by type of therapy.**

| Variables | Total | Non biological therapy | Anti-TNF therapy | Tocilizumab | Other biological therapy | *p-value* |
|---|---|---|---|---|---|---|
| Total cholesterol (mg/dL), (n) mean ± SD | (774) 204.16 ± 35.56 | (462) 201.90 ± 36.03 | (235) 207.26 ± 35.57 | (30) 217.65 ± 29.20 | (47) 202.15 ± 32.21 | 0.04 |
| Triglycerides (mg/dL), (n) mean ± SD | (770) 107.16 ± 55.21 | (458) 103.13 ± 52.20 | (235) 110.04 ± 57.62 | (30) 130.60 ± 76.25 | (47) 117.05 ± 51.71 | 0.01 |
| LDL-c (mg/dL), (n) mean ± SD | (724) 122.76 ± 32.92 | (433) 121.17 ± 33.53 | (218) 126.13 ± 31.65 | (29) 128.43 ± 28.82 | (44) 117.95 ± 37.91 | 0.16 |
| HDL-c (mg/dL), (n) mean ± SD | (759) 61.29 ± 17.15 | (452) 61.14 ± 17.27 | (230) 60.69 ±16.22 | (30) 64.30 ± 16.71 | (47) 63.71± 20.58 | 0.53 |
| Apo AI (mg/dL), (n) mean ± SD | (591) 162.99 ± 31.36 | (360) 164.59 ± 33.04 | (175) 159.76 ± 27.47 | (24) 165.5 ± 28.66 | (32) 160.94 ± 33.58 | 0.37 |
| Apo B (mg/dL), (n) mean ± SD | (603) 94.42 ± 23.97 | (367) 93.93 ± 24.72 | (179) 96.02 ± 22.38 | (24) 97.77 ± 21.94 | (33) 88.62 ± 25.13 | 0.35 |
| Atherogenic index, (n) mean ± SD | (759) 3.60 ± 1.31 | (452) 3.59 ± 1.44 | (230) 3.63 ± 1.06 | (30) 3.61 ± 1.12 | (47) 3.49 ± 1.28 | 0.92 |
| Lipoprotein (a) (mg/dL), (n) median, [p25-p75] | (441) 15.5 [6-34.7] | (265) 16.7 [7.2-40] | (131) 15.4 [6-32.3] | (21) 8.5 [6-15.5] | (24) 10.8 [2.2-26.3] | 0.05 |
| Lipoprotein (a) >50 mg/dL, n (%) | 72 (16.33) | 50 (18.87) | 19 (14.5) | 1 (4.76) | 2 (8.33) | 0.04 |

TNF: tumor necrosis factor; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; Atherogenic index: total cholesterol/HDL-c; Apo: apolipoprotein.

**Table 3** shows the results of the multivariate analysis. After adjusting for confounding factors, patients treated with biologic therapy reached lower plasma concentrations of Lp(a) than those not undergoing biologic therapy. However, only the subgroup of patients treated with TCZ achieved statistically significant differences when compared with those not receiving biologic therapy (β-coefficient: -0.303, 95% confidence interval (CI): -0.558 to -0.047; p=0.02). The results demonstrated a positive association between LDL-c and Lp(a) (β-coefficient: 0.002, 95% CI: 0.0004 to 0.004; p=0.01), and

a negative association between the concentrations of Lp(a) and triglycerides (β-coefficient: -0.002, 95%CI -0.003 to -0.0007; p =0.001).

**Table 3. Multivariate analysis of Lp(a) levels in patients with RA.**

Multivariate linear regression adjusted for confounding factors (age, sex, hypercholesterolemia, LDL-c, triglycerides, ESR, disease duration and DMARD administration). Outcome variable: Log Lp(a). CI: confidence interval; TNF: tumor necrosis factor; LDL-c: low-density lipoprotein cholesterol; CRP: C-reactive protein; DMARD: Disease-modifying antirheumatic drugs.

| **Variables** | **Regression beta Coefficient (95% CI)** | ***p-value*** |
|---|---|---|
| Type of therapy (ref. non-biologic therapy) | | |
| Anti-TNF therapy | -0.118 (-0.246 to 0.010) | 0.07 |
| Tocilizumab | -0.303 (-0.558 to -0.047) | 0.02 |
| Other biologic therapies | -0.182 (-0.425 to 0.061) | 0.14 |
| Age | -0.0004 (-0.004 to 0.005) | 0.86 |
| Sex (ref. male) | -0.065 (-0.198 to 0.068) | 0.34 |
| Hypercholesterolemia (ref. no) | 0.165 (0.034 to 0.296) | 0.01 |
| LDL-c (mg/dL) | 0.002 (0.0004 to 0.004) | 0.01 |
| Triglyceride (mg/dL) | -0.002 (-0.003 to -0.0007) | 0.001 |
| Tender joint count | -0.006 (-0.020 to 0.008) | 0.40 |
| CRP (mg/L) | 0.001 (-0.002 to 0.005) | 0.44 |
| Disease duration (years) | 0.004 (-0.002 to 0.011) | 0.20 |
| DMARD (ref. no) | 0.122 (-0.035 to 0.279) | 0.13 |

## DISCUSSION

The results from the present study show that TCZ-treated RA patients followed-up at rheumatology-out-patient clinics have lower plasma concentrations of Lp(a) than RA patients not treated with biologics.

The relationship between alterations in conventional lipid profiles and inflammation in patients with RA is well known (14). However, despite the fact that Lp(a) exerts atherogenic and prothrombotic effects (3), the presence of hyperlipoproteinemia(a) in RA has not received sufficient attention (2, 15). This may be due in part to the lack of an effective pharmacological treatment for hyperlipoproteinemia(a) (16), and also

because plasma Lp(a) is not recommended as a general screening test for assessing CV risk in the general population. Nonetheless, Lp(a) assessment is indicated in people with a high CV risk or a strong family history of premature atherothrombotic disease (17).

Due to the presence of chronic inflammation, the relationship between CV disease and lipid levels in patients with RA appears to be different from that observed in the general population (18). In this regard, lipoprotein abnormalities described in RA patients improve with effective anti-rheumatic treatment as a result of the reduction in inflammation (7). Nevertheless, the mechanisms involved in this process are far from being completely understood. Although some studies have shown that methotrexate alone, or in combination with an anti-TNF, may lead to a significant reduction of Lp(a) levels in RA (19), a former study of our group disclosed that Lp(a) levels remain consistently elevated in RA despite antirheumatic therapy (including glucocorticoids, conventional DMARDs and anti-TNF therapy) (2).

The introduction of biologic therapies targeting specific inflammatory mediators different from anti-TNF agents has been an important step forward in the management of RA. The results of the present study did not show statistically significant differences in the Lp(a) levels between RA patients treated with anti-TNF therapy and those not receiving biologic therapy. Unlike these biologic agents, it is worth noting that TCZ therapy was associated with low plasma concentrations of Lp(a) in our patients with RA, and that this association remained statistically significant after adjusting for potentially confounding factors.

To the best of our knowledge, this association has only been assessed in two studies (9,10). In this regard, Schultz et al. (9) studied 11 patients with rheumatic diseases (without describing the specific diagnosis), and found that the inhibition of IL-6 signaling reduced Lp(a) plasma concentrations. This effect was observed in the first

month of treatment and remained present at the third month. McInnes et al. (10), in a multicenter study involving 132 patients randomized in two arms; placebo plus methotrexate and TCZ plus methotrexate, described a 37% reduction in Lp(a) concentrations in TCZ-treated patients. More recently, Gabay et al. compared changes in lipids in RA patients treated with tocilizumab and adalimumab in a post-hoc analysis (20). They found that tocilizumab yielded higher increase of LDL-c and HDL-c levels than adalimumab. However, Lp(a) only decreased with tocilizumab (20).

Anti-rheumatic therapies increase TC, HDL-c, LDL-c and TG to variable degrees in patients with RA (18). This is especially true for patients treated with the anti-IL-6-receptor TCZ. Nevertheless, in the majority of TCZ-treated patients there is no increase in the atherogenic index (TC/HDL-c), and patients experience a good response to treatment with lipid lowering agents (21). In keeping with that, the present study disclosed a significant increase of TC and TG levels in RA patients undergoing TCZ therapy. LDL-c and HDL-c were also slightly elevated when compared with RA patients who were not treated with biologic therapy, although the differences did not reach statistical significance. Moreover, as previously reported, no significant differences in the atherogenic index were found.

Additional findings from our study were the positive association between Lp(a) and LDL-c and the negative association between Lp(a) and TG. These findings have also previously been described (22). The positive correlation between the LDL-c and Lp(a) could be explained, in part, because the value of the concentration of Lp(a) was included in the value of LDL-c. This is also consistent with the fact that every particle of Lp(a) contains a particle of LDL. The inverse correlation between the serum concentration of triglycerides and Lp(a) has also been described in several observational studies, though the underlying mechanism has not been elucidated (22, 23). It has been

postulated that a common mechanism related to the metabolic syndrome could be implicated in lowering Lp(a) in patients with hypertriglyceridemia (24).

Despite the fact that TCZ is associated with an increase in lipids, the use of this biologic agent has a favorable effect on lipid metabolism. With respect to this, TCZ improves the functionality of HDL-cholesterol. This is due to beneficial effects on its structural composition, moving from proinflammatory to anti-inflammatory particles (10, 25).As mentioned before, this study shows that TCZ displays low plasma concentrations of Lp(a), which is increasingly recognized as a risk factor signaling the development of coronary heart disease (4). In this regard, a study of 1,153 individuals revealed that Lp(a) levels were increased in those with elevated IL-6 serum concentrations (26). In the same study transcriptomic analyses revealed that the commonly found IL-6 response genes correlated with apo(a) gene *LPA* expression in human liver *in vivo*. Moreover, the authors found that TCZ inhibited IL-6-induced expression of *LPA* and specifically inhibited *LPA* promoter activity in human hepatocytes on a molecular level (26). Therefore, the association between IL-6 inhibition and lower levels of Lp(a) appears to be regulated by genetic mechanisms, specifically to regulation of the genetic expression of apo(a), the main protein of this lipoprotein.

The strong association between elevated Lp(a) levels and increased CV disease/risk suggests that the former, like elevated LDL-c, is causally associated with premature CV disease (27). Since recent studies have shown a high frequency of carotid plaques in RA patients included in the category of moderate CV risk we think that Lp(a) assessment might be considered in the study of patients with chronic inflammatory diseases (29), not only in those patients with a high CV risk, familial hypercholesterolemia, or a family history of premature CV disease.

There are a number of potential limitations in our study. First, the subgroup of RA patients undergoing TCZ therapy was relatively small. Nevertheless, the significant association between TCZ and lower plasma concentrations of Lp(a) was reinforced after adjusting for potential confounding factors. Second, we could not send all of the samples to a single reference laboratory to determine the lipid parameters. Therefore, we performed a statistical analysis that attempted to minimize the impact of possible variations in the results from the different centers. Finally, another point of potential concern is the cross-sectional nature of our analysis. Nevertheless, our results support an effect of the IL-6 blockade on Lp(a) that makes TCZ different from anti-TNF therapy.

## CONCLUSIONS

In conclusion, the results of the CARMA cohort confirm the claim that the use of anti-IL6 receptor TCZ therapy is associated with low plasma concentrations of Lp(a). This association may have important clinical implications in the cardiovascular profile of patients with RA.

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**LIST OF ABBREVIATIONS**

Rheumatoid Arthritis: RA; Cardiovascular: CV; Lipoprotein(a): Lp(a); Low-density lipoprotein cholesterol: LDL-c; Apolipoprotein B100: apoB100; Apolipoprotein (a): apo(a); Interleukin-6: IL-6; CARdiovascular in rheumatology: CARMA; Spanish Society of Rheumatology: SER; TNF: tumor necrosis factor; Tocilizumab: TCZ; Rheumatoid factor RF; Anti-cyclic citrullinated peptide antibodies: ACPA; Erythrocyte sedimentation rate: ESR; C-reactive protein: CRP; Disease Activity Score including 28 joints and erythrocyte sedimentation rate: DAS28-ESR; Health Assessment

Questionnaire: HAQ; Total cholesterol: TC; Triglycerides: TG; High-density lipoprotein cholesterol: HDL-c; Apolipoprotein AI: apo AI; apolipoprotein B: apo B; atherogenic index: TC/HDL-c; SD: standard deviation; BMI: body mass index; IHD: ischemic heart disease; DMARD: disease-modifying antirheumatic drugs; NSAID: non-steroidal anti-inflammatory drugs; ACE: angiotensin converting enzyme; ARBs: angiotensin II receptor blockers;

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was performed following the principles outlined in the Helsinki Declaration and the study protocol was approved by the Ethics Committee for Clinical Research of Galicia, Spain.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

## AUTHORS' CONTRIBUTIONS

MCGG, MAMM and MAGG performed to the design of the study. MAMM and FSA conducted the data analysis and MCGG, MAMA, SC and MAGG contributed the data interpretation and drafted the manuscript. CGJ, JL and FDG helped interpret the data and strengthen the manuscript. MAGG helped design and developed the CARMA project, assisted in data interpretation, and was responsible for the final draft of the manuscript. All authors read and approved the final manuscript.

## Highlights

1. RA on biological therapies, mainly anti-IL6, displays lower lipoprotein (a) levels.

2. Patients with TCZ show higher TC and TG levels, without differences in the atherogenic index.

3. TCZ-treated patients in this study had lower disease activity but poorer scores on HAQ.