Obesity and response to biological therapy in rheumatoid arthritis: the role of body mass index and adipose tissue cytokines

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Abstract

Objective

To analyse the role of body mass index (BMI) in the clinical response to biologic disease-modifying anti-rheumatic drugs (bDMARDs) in patients with rheumatoid arthritis (RA). To perform an in-depth analysis of the pathophysiology of obesity by assessing serum adipokine levels and their potential changes according to treatment.

Methods

This study involved 105 patients with RA starting tumour necrosis factor inhibitors (TNFi) or tocilizumab (TCZ). Patients were classified according to BMI as normal-weight and overweight/obesity. The clinical response to treatment was assessed by Clinical Disease Activity Index (CDAI) 6 months after initiation of bDMARDs. Serum adipokines (leptin and adiponectin) were determined using a commercial immunoassay kit in samples obtained before initiation of bDMARDs and after 6 months of treatment.

Results

A correlation was observed between BMI and disease activity and between BMI and serum adipokines. Sixty percent of patients achieved low disease activity (LDA)/remission: 45 patients in TNFi group (64.2%) and 18 (51.4%) in TCZ group. In TNFi group, patients who did not attain LDA/remission had a higher BMI (kg/m^2) ([28.7±5.1] vs. [24.5±4.6], p=0.001) and baseline CDAI (26.3 [17.4-33.9] vs. 19.8 [14.0-28.8], p<0.03). However, no differences in BMI or baseline CDAI were observed between patients who achieved LDA after 6 months in TCZ group.

Conclusion

Obesity influences the extent of LDA/remission in patients treated with TNFi, but not in patients treated with TCZ, probably because of underlying pathophysiological mechanisms intrinsic to the production of proinflammatory adipokines. Therefore, therapeutic strategies with a mechanism of action other than TNF inhibition would be more suitable for obese patients.

Key words

rheumatoid arthritis, obesity, adipokines, tumour necrosis factor inhibitors, tocilizumab

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Background

In recent years, interest in the field of obesity has grown exponentially due to the increasing prevalence of this comorbid condition (1). Obesity predisposes to metabolic and cardiovascular diseases, but has also been linked to chronic inflammatory diseases: the behavior of adipose tissue as an endocrine organ gives it a major role in the regulation of metabolism and immune and inflammatory processes (2).

The progressive and excessive accumulation of fat in obesity leads to substantial changes in the quantity and phenotype of the immune cells residing in white adipose tissue (WAT). These changes lead to an increase in the number and activity of some cells, especially macrophages, neutrophils, T lymphocytes (Th17), and B lymphocytes, and a decrease in others, such as eosinophils and some subtypes of T lymphocytes (Th2 and Treg) (3). Furthermore, both adipocytes and immune cells infiltrating WAT secrete cytokines that help to perpetuate the inflammatory status. Therefore, WAT is capable of secreting and releasing cytokines such as tumour necrosis factor α (TNF-α) and IL-6 in a similar way to inflammatory diseases such as rheumatoid arthritis (RA). It also releases adipose tissue cytokines (adipokines, *e.g.* leptin, visfatin, and resistin) (4), most of which have proinflammatory properties associated with obesity (5, 6).

Data from studies on metabolic conditions show that a higher body mass index (BMI) is directly related to increased production of leptin, which has classically been considered a proinflammatory adipokine, and to reduced production of adiponectin, which has anti-inflammatory effects (7). As in other immune-mediated inflammatory diseases, data from some studies support the involvement of adipokines in the pathophysiology of RA, although the exact role of these cytokines in disease progression and response to treatment remains unclear (8, 9).

Therefore, the aim of this study was to analyse the role of BMI in the clinical response to biological treatments in RA patients and to analyse in depth the pathophysiology of obesity by assessing serum adipokine levels and potential changes in these levels according to treatment.

Patients and methods

The study population comprised patients with RA in the prospective biological cohort of the "Rheumatoid Arthritis La Paz University Hospital" (RA-Paz) registry between January 2000 and December 2020. The study was approved by La Paz Ethics Committee (PI-4596).

The Rheumatoid Arthritis La Paz University Hospital (RA-Paz) registry is a database of all patients who have received, or who are receiving, treatment with biologic disease-modifying antirheumatic drugs (bDMARDs). RA-Paz enables rheumatologists to include clinical information on RA patients from initiation of bDMARD treatment and during follow-up, with monitoring of clinical response and adverse events every 6 months (10).

The inclusion criteria were as follows: age ≥18 years; RA according to the 1987 ACR or 2010 ACR/EULAR classification criteria; active disease; and treatment with TNF inhibitors (TNFi) or anti-IL6R (tocilizumab) at standard doses. Patients were selected 1:1 according to their BMI: normal weight (19-24.9 kg/m^2) and overweight/obesity (≥25 kg/m^2). This selection was made to obtain groups that were statistically comparable according to BMI.

Data collection

Data were collected immediately before initiation of TNFi or tocilizumab (TCZ) as follows: demographic characteristics (age, sex, BMI, smoking habit), age at diagnosis of RA, age at initiation of bDMARDs, previous and concomitant treatments (corticosteroids and conventional synthetic [csDMARDs]), and laboratory parameters such as rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA). C-reactive protein (CRP), erythrocyte sedimentation rate, and serum leptin and adiponectin levels were assessed at baseline and after 6 months of treatment.

Assessment of clinical disease activity and response to treatment

The Clinical Disease Activity Index

(CDAI) was recorded at baseline and after 6 months of therapy with bDMARDs. The CDAI was used instead of the Disease Activity Score-28 (DAS28) in order to avoid the use of indexes containing acute phase reactants, given the effect of IL-6 inhibition on CRP.

At 6 months, patients were classified according to response to treatment (based on the CDAI) into 2 groups: patients who achieved low disease activity/remission (LDA=CDAI≤10) and patients who did not (No-LDA=CDAI>10).

Measurement of serum adipokines

Commercial immunoassay kits were used to measure serum leptin and adiponectin obtained at baseline and at 6 months (Human Leptin ELISA kit, EZHL-80SK and Human Adiponectin ELISA kit, EZHADP-61K, Merck Millipore, S.A.S.), according to the manufacturer's instructions. All samples were analysed in duplicate and quantified relative to a standard curve.

Statistical analysis

A descriptive analysis was performed. Qualitative variables are reported as absolute numbers and frequencies; quantitative variables are reported as mean and standard deviation (SD) or median and interquartile range (IQR), depending on whether data were normally distributed or not. Differences between qualitative variables were assessed using the chi-square and Fisher exact test; differences between quantitative variables were assessed using the *t*-test, Mann-Whitney test, and Wilcoxon test. Correlations between adipokines and other quantitative variables were assessed using the Pearson and Spearman coefficients. *p*-values <0.05 were considered statistically significant. The statistical analysis was performed using IBM SPSS 21.0.

Results

Baseline clinical and sociodemographic characteristics

In total, 105 RA patients were included from the RA-Paz registry: 70 had started TNFi (66.6%) and 35 TCZ (33.4%). The route of administration of TC Zwas only intravenous; among patients treated with TNFi, 35.7% received intravenous infliximab and 64.3% subcutaneous agents (adalimumab, etanercept, golimumab, and certolizumab).

Patients' characteristics before starting bDMARDs are shown in Table I. No differences were found between the groups for age, sex, disease duration, smoking habit, use of concomitant csDMARDs and corticosteroids, dosage of methotrexate, and presence of RF and/or ACPA. We observed significant differences in the number of patients who had not previously received bDMARDs. In this respect, 85.7% of patients who received TNFi were treatment-naïve compared with 62.9% of those who re-

Table I. Baseline clinical and demographic characteristics.

Variable	Total (n=105)	TNFi (n=70)	Tocilizumab (n=35)	*p*-value
Age mean (SD)	56.2 (12.9)	56.1 (13.3)	56.7 (12.3)	0.80
Sex (female) n (%)	85 (81.0)	58 (82.9)	27 (77.1)	0.32
Disease duration (years) mean (SD)	9.9 (7.9)	9.0 (7.6)	11.6 (8.3)	0.11
bDMARD-naïve n (%)	73 (69.5)	60 (85.7)	22 (62.9)	**0.001**
Smoking habit n (%)				
Current	20 (19.2)	13 (18.8)	7 (20.0)	0.27
Past	31 (29.8)	24 (34.8)	7 (20.0)	
Never	53 (50.5)	32 (46.4)	21 (60.0)	
BMI (kg/m^2) mean (SD)	26.1 (4.9)	26.0 (5.1)	26.0 (4.6)	0.99
Obesity n (%)	52 (49.5)	34 (48.6)	18 (51.4)	0.47
Concomitant cDMARDs n(%)	101 (96.2)	69 (98.6)	32 (91.4)	0.11
Concomitant MTX n(%)	69 (65.7)	49 (70.0)	20 (57.1)	0.13
MTX dose (mg) median (IQR)	20 (12.5-25)	20 (15-25)	15 (10-20)	0.06
Concomitant CS n (%)	61 (58.1)	41 (58.6)	20 (57.1)	0.52
CS dose (mg) median (IQR)	5 (0-5)	5 (0-5)	5 (0-5)	0.37
RF positive (IU/mL) n (%)	77 (73.3)	52 (74.3)	25 (71.4)	0.41
ACPA positive (UI/mL) n (%)	83 (79.0)	55 (78.6)	28 (80.0)	0.55
CRP b (mg/L) median (IQR)	6.7 (2.2-21.2)	6.5 (2.2-21.0)	6.7 (2.1-22.7)	0.63
CDAI b median (IQR)	22 (15.2-32.8)	21 (14.9-31.7)	25 (17.0-38.0)	0.11

bDMARD: biologic disease-modifying anti-rheumatic drug; BMI: body mass index; cDMARD: conventional disease-modifying anti-heumatic drug; MTX: methotrexate; CS: corticosteroids; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; CRP: C-reactive protein; CDAI: Clinical Disease Activity Index. SD: standard deviation; IQR; interquartile range.

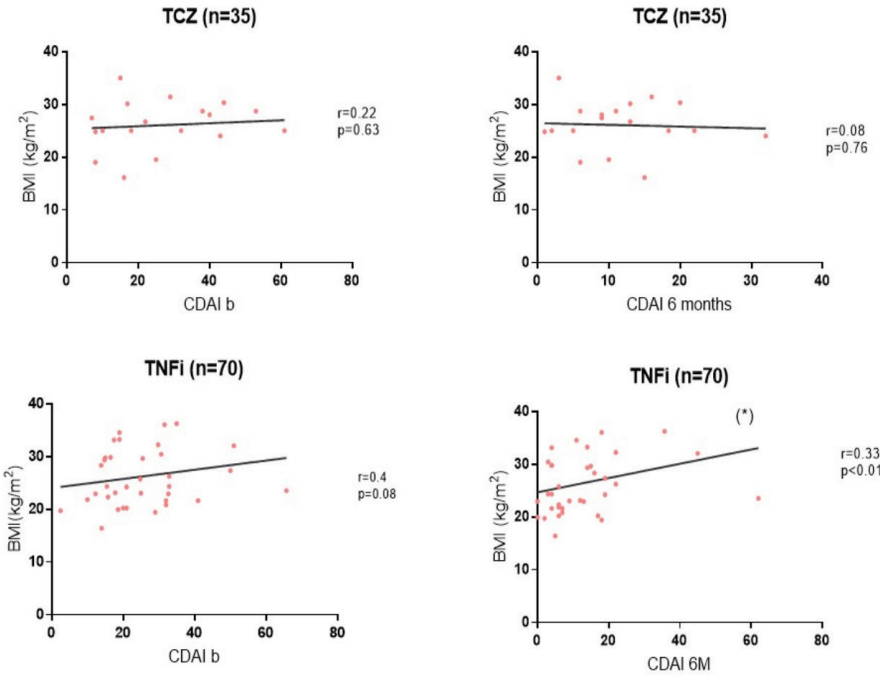

Fig. 1. Correlation between CDAI and BMI at baseline and at 6 months for both treatments.

Table II. Differences between clinical and laboratory parameters: LDA vs. No-LDA in the TNFi and tocilizumab groups.

Variable	TNFi (n=70)			Tocilizumab (n=35)		
	LDA (n=45)	No-LDA (n=25)	*p*-value	LDA (n=18)	No-LDA (n=17)	*p*-value
Age mean (SD)	55.5 (13.0)	56.9 (14.1)	0.67	58.6 (9.9)	54.6 (14.5)	0.34
Sex (female) n(%)	36 (80.0)	22 (88.0)	0.30	13 (72.2)	14 (82.4)	0.38
Disease duration mean (SD)	8.5 (7.2)	10.0 (8.4)	0.43	13.2 (9.2)	10.0 (6.6)	0.25
bDMARD naïve n(%)	39 (86.7)	21 (84.0)	0.51	7 (38.9)	6 (35.3)	0.55
Smoking habit n (%)						
-Current	7 (15.6)	6 (24.0)		4 (22.2)	3 (17.6)	
-Past	18 (40.0)	6 (24.0)	0.39	5 (27.8)	2 (11.8)	0.40
-Never	20 (44.4)	12 (48.0)		9 (50)	12 (70.6)	
BMI (kg/m^2) mean (SD)	24.5 (4.6)	28.7 (5.1)	**0.001***	25.1 (4.2)	27.1 (4.9)	0.21
Obesity n (%)	16 (35.6)	18 (72.0)	**0.004***	8 (44.4)	10 (58.8)	0.30
ACPA (+) (IU/mL) n (%)	37 (82.2)	18 (72.0)	0.27	16 (88.9)	12 (70.6)	0.17
RF (+) (IU/mL) n (%)	32 (72.7)	20 (80.0)	0.35	13 (72.2)	12 (70.6)	0.64
Concomitant csDMARD n (%)	45 (100)	24 (96.0)	0.35	15 (83.3)	17 (100)	0.12
Concomitant MTX n (%)	30 (66.7)	19 (76.0)	0.29	9 (50.0)	11 (64.7)	0.29
MTX dosage (mg) median (IQR)	20 (12.5-25)	20 (17.5-25)	0.26	15 (0-17.5)	20 (15-20)	0.18
Concomitant CS n (%)	25 (55.6)	16 (64.0)	0.33	12 (66.7)	8 (47.1)	0.21
CS dosage (mg) median (IQR)	5 (0-5)	5 (0-5)	0.68	5 (2.5-5)	5 (0-5)	0.57
CDAI b median (IQR)	19.8 (14.0-28.8)	26.3 (17.4-33.9)	**0.03***	25.0 (13.7-38.0)	29.0 (19.0-39.5)	0.4
CRP b (mg/L) median (IQR)	6.0 (1.7-21.5)	6.8 (3.1-20.2)	0.51	8.2 (1.8-34.9)	5.8 (3.3-14.8)	0.50
CRP 6 m (mg/L) Median (IQR)	1.3 (0.75-6.1)	3.0 (0.9-8.1)	0.13	0.8 (0.3-3.6)	0.8 (0.4-1.4)	0.85
		Adipokines				
Leptin b (ng/mL) median (IQR)	15.5 (7.5-22.9)	25.7 (13.8-38.5)	**0.01***	18.3 (8.1-22.5)	11.3 (8.9-27.2)	0.48
Leptin 6 m (ng/mL) median (IQR)	15.7 (8.2-26.4)	30.8 (18.2-41.4)	**0.001***	17.5 (7.8-26.0)	13.2 (5.4-25.9)	0.61
Adiponectin b (ng/mL) median (IQR)	19510 (15090-24765)	20170 (12175-26470)	0.67	17515 (11890.5-41382.5)	14060 (9290.5-21755.0)	0.54
Adiponectin 6 m (ng/mL) Median (IQR)	19130 (14870-26890)	16350 (11615-23195)	0.09	19985 (9201-39597.5)	17820 (11510-28840)	0.85

bDMARD: biologic disease-modifying anti-rheumatic drug; BMI: body mass index; cDMARD: conventional disease-modifying anti-rheumatic drug; MTX: methotrexate; CS: corticosteroids; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; CRP: C-reactive protein; CDAI: Clinical Disease Activity Index. SD: standard deviation; IQR; interquartile range.
*Statistically significant ($p<0.05$).

ceived tocilizumab *(p*=0.01), although all patients received TNFi or TCZ as their first- or second-line treatment. As for BMI, no differences were observed between the treatments or for the frequency of obesity. Baseline disease activity measured by CDAI was similar in both groups (Table I).

Association between BMI and disease activity

No correlation between disease activity and BMI was found at baseline. However, after 6 months of treatment, a positive correlation was recorded between CDAI and BMI in the TNFi group (r=0.33; *(p*=0.006). However, no correlation was found at 6 months in the TCZ group (Fig. 1).

Association between BMI and serum adipokines

A significant positive correlation with BMI was found for leptin levels, overall and by treatment group, both at baseline (total: r=0.52, $p<0.01$; TNFi: r=0.54, $p<0.01$; TCZ: r=0.51, $p<0.01$) and at 6 months of treatment (total: r=0.57, $p<0.01$; TNFi: r=0.57, $p<0.01$; TCZ: r=0.42, $p=0.01$).

A significant negative correlation with BMI was recorded for adiponectin levels at baseline (total: r=-0.31, $p<0.01$; TNFi: r=-0.27, $p=0.02$; TCZ: r=-0.29, $p=0.05$) and at 6 months of treatment globally and in the TNFi group (total: r=-0.33, $p<0.01$; TNFi: r=-0.33, $p=0.02$; TCZ: r=-0.23, $p=0.17$).

Adipokine levels in the overall sample and by treatment are shown in Table I. In this regard, leptin levels were significantly higher at 6 months of treatment in the TNFi group than in theTCZ group (19.2 [10.9-32.2] *vs*. 14.2 [6.3-23.7]; $p=0.04$). No differences were observed for baseline adipokines (leptin and adiponectin) or adiponectin alone at 6 months of therapy (Table I).

Association between BMI and serum adipokines in response to treatment

After observing the correlation between BMI and disease activity and between BMI and serum adipokines, we analysed the association between these parameters and response to treatment in both groups.

Sixty-three of 105 patients (60%) achieved LDA/remission (45 patients in the TNFi group [64.2%] and 18 patients [51.4%] in the tocilizumab group).

In the TNFi group, higher BMI (kg/m^2) and baseline CDAI values were recorded for patients who did not attain LDA/remission (BMI, [28.7±5.1] *vs*. [24.5±4.6], $p=0.001$; CDAI, 26.3 [17.4–33.9] *vs*. 19.8 [14.0–28.8], $p<0.03$). However, no differences were observed in BMI or baseline CDAI among patients who achieved LDA/remission after 6 months in the TCZ group (Table II).

An increase in leptin levels after 6 months of TNFi treatment was observed in the patients in the TNFi group who did not achieve LDA/remission, although no differences in adiponectin levels were observed in this group (Table II). Interestingly, we found statistically significant differences in leptin levels when stratifying this group by response to treatment, that is, levels were higher in patients who did not achieve LDA either at baseline (25.7 [13.8–38.5] *vs*. 15.5 [7.5-22.9], *p*=0.01) or at 6 months (30.8 [18.2–41.4] *vs*. 15.7 [8.2–26.4], *p*=0.001) (Fig. 2). However, with regard to the administration route, no differences in disease activity, BMI, or adipokines were observed between intravenous and subcutaneous treatments.

In the TCZ group, on the other hand, we observed a decrease in leptin levels between baseline (16.4 [8.5–26.4]) and 6 months (14.2 [6.4–23.7]) (Table II). However, we did not find statistically significant differences in leptin or adiponectin levels between patients who achieved LDA and those who did not (Fig. 2).

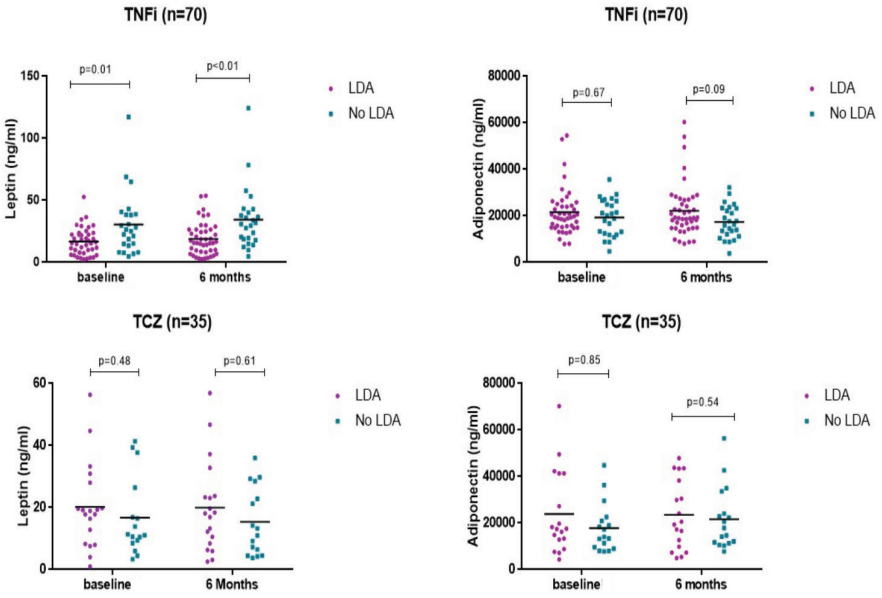

Fig. 2. Leptin and adiponectin levels with TNFi and tocilizumab.

Discussion

Our results show that BMI is directly related to clinical response 6 months after initiation of biological treatment with TNFi, independently of the administration route, and that this effect is not observed in patients receiving intravenous TCZ. In this sense, we found that fewer obese patients receiving TNFi achieved LDA/remission after 6 months of therapy. Further analysis of adipokines indicates that leptin is the adipose tissue cytokine involved in the response to TNFi in obese patients. In contrast, these cytokines do not appear to influence the response to TCZ.

The impact of BMI on the control of disease activity in rheumatic diseases has been widely reported in the literature. Most studies suggest that obesity and overweight reduce the likelihood of achieving LDA or remission in affected patients (11, 12). Moreover, a recent study showed that substantial weight loss in patients with RA and psoriatic arthritis, regardless of the treatment received, is associated with an improvement in disease activity (13). In the present study, BMI seemed to influence the response to treatment with TNFi but not with TCZ. These results are in line with those of other studies, where TNF blocking was impaired in obese patients, but inhibition of T cell co-stimulation and IL-6 receptor blocking were not affected by obesity (14-16). However, a recent study by Schäfer *et al*. (17) suggests that obesity adjusted for sex also has a negative impact on the effectiveness of TCZ .

In-depth analysis of the pathophysiological mechanisms underlying obesity revealed that serum leptin levels were higher in patients who did not respond to treatment with TNFi. These levels were directly correlated with disease activity at 6 months of treatment. This finding is consistent with those of other studies in which higher leptin levels are related to a higher DAS-28 score, although they do not assess the correlation between these levels and clinical response (18-20). In our study, serum leptin levels did not change in patients who responded to TNFi; on the contrary, they remained elevated or even increased after 6 months in patients who did not achieve LDA/remission with TNFi. However, these differences are not statistically significant. Leptin levels have been reported to be unaffected after treatment with TNFi (21, 22), although they are correlated with BMI in patients with RA, probably because, in both RA and obesity, TNF levels are increased and may generate a synergistic effect with pro-inflammatory cytokines, such as leptin, which hinders an adequate response to this type of bDMARD (23).

Regarding TCZ we found that leptin levels remained unaffected according to response to treatment. Leptin levels decreased from baseline to 6 months among patients treated with TCZ, although the difference was not statistically significant. This result is in line with those reported by Hoffman *et al*. (24), who found no statistically significant differences in leptin levels when patients were stratified into responders and non-responders to tocilizumab according to DAS-28 or CDAI adjusted for BMI. On the other hand, Pulito-Cueto *et al*. (25) found a significant decrease in leptin levels after treatment with TCZ irrespective of BMI. While this decrease was not related to disease activity, it may support other beneficial effects in comorbidities associated with RA (25, 26), such as diabetes and obesity. Therefore, blockade of the IL-6 signalling pathway might be more effective than blockade of TNF for treatment of metabolic comorbidities in patients with RA (27).

Our findings for BMI and adipokines could be related to the route of drug administration, since TCZ was administered intravenously and TNFi both

intravenously and subcutaneously. Therefore, leptin levels may be affected by the need to adjust doses for weight. However, we did not observe differences between the subcutaneous and intravenous routes in patients treated with TNFi; any differences may be due to the mechanism of action and not to the pharmacokinetics or bioavailability of the drug. Binding of IL-6 to mIL-6R or sIL-6R forms a complex, which associates with the signalling receptor protein gp130, leading to activation of intracellular signalling pathways, such as the Janus kinase/signal transducer and activator of transcription (Jak/STAT) pathways. Interestingly, the leptin receptor is similar to the signalling protein gp130, which exerts its biological activity through activation of Jak/STAT, thus contributing to regulation of body weight and leptin sensitivity (6, 28, 29). While TNF-α enhances leptin production and positive feedback has been demonstrated between these 2 cytokines, they do not share a specific signalling pathway, as occurs with leptin and IL-6. Therefore, treatment with an IL-6R inhibitor such as TCZ would be more effective for regulating inflammation in obese patients with RA.

Adiponectin has traditionally been considered an adipokine with anti-inflammatory properties, although its role in RA is more controversial (8). We recorded no changes and no association with achievement of LDA for TNFi or for TCZ. Data from the literature indicate that adiponectin is less sensitive to changes associated with bDMARDs (21, 24, 30, 31).

Our findings provide further insight into the pathophysiological mechanisms underlying obesity and its influence on the control of inflammation in RA. Pairing the sample 1:1 as normal weight/overweight made it possible to eliminate obesity as a confounding factor when determining adipokines. Thus, a homogeneous and comparable sample enabled us to identify and to assess the influence of these biomarkers on disease activity. In addition, ours is one of the few studies to directly compare BMI and WAT cytokines and assess their effect on response to bDMARDs.

Our study is limited by its small sample size and by the fact that we did not measure more inflammatory cytokines implicated in obesity and RA. Future studies should address this challenge and analyse other bDMARDs with different mechanisms of action.

Conclusions

Obesity influences the extent of LDA/remission in patients treated with TNFi, but not in patients treated with intravenous TCZ. This may be due to the pathophysiological mechanisms underlying the production of proinflammatory cytokines by WAT. Therefore, therapeutic strategies with a mechanism of action other than inhibition of TNF would be more suitable for obese patients.

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