Obesity and adipose tissue cytokines in rheumatoid arthritis treated with IL-6 inhibitors: does the route of administration matter?

Sirs,

Obesity is associated with the response to biologic disease-modifying anti-rheumatic drugs (bDMARDs) in rheumatoid arthritis (RA) (1). In a previous work published by our group, we found that higher body mass index (BMI) (2) and cytokines from white adipose tissue (adipokines) were related to a lack of response in patients treated with TNF inhibitors but not intravenous IL6R-inhibitors. In this study, we aimed to analyse if BMI and serum adipokines were related to disease activity regarding the route of administration of IL6-R inhibitors.

Sixty-five RA patients were included: 47 who started iv therapy (72.3%) and 18 with sc therapy (27.7%). The data collected before initiation of IL6R-inhibitor were as follows: demographic characteristics (age, sex, smoking habit), age at diagnosis of RA, age at initiation of bDMARDs, and previous and concomitant treatments (corticosteroids and conventional synthetic [csDMARDs]). BMI was collected as a quantitative variable and categorised as normal weight (BMI <25 kg/m^2) or overweight/obesity (BMI >25 kg/m^2). The Clinical Disease Activity Index (CDAI) was recorded at baseline and after 6 months of treatment. Serum leptin and adiponectin were measured using commercial immunoassay kits at baseline and 6 months. The proportion of patients with normal weight and overweight/obesity was similar between the sc and iv groups (61.1% *vs*. 53.2%, p=0.38). No correlation was observed at baseline between BMI and disease activity overall or by route of administration (total: r=0.04, p=0.78; iv: r=0.06, p=0.63; sc: r=0.14, p=0.46) or after 6 months (total: r=0.03, p=0.79; iv: r=0.02, p=0.88; sc: r=0.09, p=0.20). Leptin levels in both groups were very similar at baseline and at 6 months of treatment. Patients who started sc therapy had higher baseline levels of adiponectin; however, no differences were observed after 6 months. Regarding changes in adipokine profile between baseline and 6 months, we observed a decrease in leptin levels and an increase in adiponectin levels in both groups. However, these differences were not statistically significant (Table I). And, no association was found between adipokine levels and disease activity.

Our results show BMI and adipokine profile are not related to clinical disease activity during the first 6 months of treatment and that leptin and adiponectin levels in patients treated with IL6R- inhibitors remained unchanged regardless of the route of administration (iv or sc).

Other studies have analysed the influence of BMI in patients taking sc IL6R-inhibitors.

Table I. Global characteristics and differences between clinical findings, demographic data, and serum adipokine levels in patients receiving IL-6R inhibitors (intravenous *vs*. subcutaneous).

Variable	Total (n=65)	IV (n=47)	SC (n=18)	p-value
Age (y)				
Current	56.5 (49–65)	56.0 (49–68)	56.5 (19–63)	0.82
At initiation of bDMARD	53.8 (45–64)	55.0 (46–64)	51.0 (40.5–58.5)	0.15
Disease duration (y)	10.0 (5.5–16.0)	10.0 (4.0–16.0)	12.5 (5.7–20.0)	0.51
bDMARD duration (y)	2.0 (0–8)	20. (0–4)	5 (0.7–8.2)	0.10
Sex (female)	53 (81.5)	39 (83.1)	14 (77.8)	0.43
Smoking habit				
Current	10 (15.4)	8 (17.5)	2 (11.1)	
Past	17 (26.2)	12 (25.5)	5 (27.8)	0.81
Non-smoker	38 (58.5)	27 (57.4)	11 (61.1)	
BMI (kg/m^2)*	26.3 (4.8)	26.6 (5.1)	26.5 (3.7)	0.50
Overweight-Obesity (BMI >25)	36 (55.4)	25 (53.2)	11 (61.1)	0.38
Previous bDMARD	40 (61.5)	26 (55.3)	14 (77.1)	0.08
Immunological parameters				
RF-positive (IU/mL)	49 (75.4)	31 (66.0)	18 (100)	**<0.01**
ACPA (IU/mL)	54 (83.1)	38 (80.9)	16 (88.9)	0.35
Concomitant MTX	43 (66.2)	30 (63.8)	13 (72.2)	0.37
MTX dosage (mg)	15 (10–20)	15 (5–20)	15 (10–20)	0.98
Concomitant CS	34 (52.3)	28 (59.6)	6 (33.3)	0.09
CDAI baseline	24.0 (17.5–35.5)	25.0 (18.0–38.0)	20.0 (13.7–25.0)	**0.03**
CDAI 6 months	9.0 (5.5–15.0)	10.0 (6.0–16.0)	7.5 (5.0–12.0)	0.27
Low disease activity	36 (55.4)	24 (51.1)	12 (66.7)	0.19
Remission	7 (10.8)	6 (12.8)	1 (5.6)	0.36
Serum adipokines				
Baseline leptin (ng/mL)	18.4 (10.5–28.1)	18.6 (10.4–30.9)	17.9 (10.1–27.4)	0.88
Baseline adiponectin (ng/mL)	20,910 (14,480–37,390)	18,310 (13,250–33,890)	28,750 (20,570–4,394)	**0.02**
Leptin at 6 months (ng/mL)	16.4 (7.8–29.3)	16.9 (7.2–29.2)	16.3 (7.6–30.7)	0.93
Adiponectin at 6 months (ng/mL)	24,160 (14,365–37,390)	20,610 (12,690–33,650)	33,350 (24,157.5–49,862.5)	0.07

y: years; 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; IU: international units; ACPA: anti-citrullinated peptide antibodies; CDAI: Clinical Disease Activity Index.
*All quantitative variables are expressed as median and interquartile range (IQR), except BMI, which is expressed as mean and standard deviation (SD).

Data from a cohort of 100 patients treated with sc tocilizumab (3) reported a negative correlation between BMI and LDA/remission when stratified by BMI groups, although the differences reported were not statistically significant. On the other hand, in an analysis of patients in the CORRONA registry, no association was observed between obesity and response to sc and iv treatment (4). Data from a pharmacodynamics and pharmacokinetics study in the SUMMACTA and BREVACTA trials showed that, with sc dosing, increased body weight was associated with lower minimum tocilizumab concentrations, so the regimen of 162 mg every 2 weeks in patients weighing >100kg resulted in less-than-therapeutic drug exposure and in clinical responses not dissimilar to those observed with placebo (5).

Regarding the serum adipokine profile, our findings agree with those reported by other studies (6, 7), showing that leptin levels decreased after 4 and 6 months of iv tocilizumab and adiponectin increase between baseline and 6 months of treatment (6). Other studies have assessed changes in adipokine levels one hour after administration of tocilizumab (8, 9) and observed a significant decrease in leptin levels but did not find changes in adiponectin levels in post-infusional measurements. As we can see, the results of these studies are controversial, perhaps owing to the heterogeneity of the populations selected and the study design. Therefore, this issue requires further investigation.

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