Response to Tocilizumab in Rheumatoid Arthritis Is Not Influenced by the Body Mass Index of the Patient

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ABSTRACT. ***Objective.*** To assess the relationship between the body mass index (BMI) and the efficacy of tocilizumab (TCZ) in patients with rheumatoid arthritis (RA).

Methods. We conducted a retrospective study in 222 patients with RA followed by 5 centers. The European League Against Rheumatism response was evaluated at 6 months. Univariate and multivariate logistic regressions were performed.

Results. No significant association between the BMI and the response to TCZ at 6 months was found after adjustment for potential confounding factors (adjusted OR 0.45, 95% CI 0.16–1.24, p = 0.13 and OR 1.19, 95% CI 0.31–4.48, p = 0.78 for BMI 25–30 kg/m^2 and BMI > 30 kg/m^2, respectively, compared to BMI < 25 kg/m^2).

Conclusion. Response to TCZ in patients with RA is not influenced by the baseline BMI, in contrast to anti-tumor necrosis factor drugs. (First Release Feb 1 2015; J Rheumatol 2015;42:580–4; doi:10.3899/jrheum.140673)

Key Indexing Terms:
TOCILIZUMAB BODY MASS INDEX RHEUMATOID ARTHRITIS RESPONSE

In the last 10 years, intensive studies on rheumatoid arthritis (RA) inflammation processes have led to the development of several biologic drugs [including tumor necrosis factor (TNF) blockers, abatacept, tocilizumab (TCZ), and rituximab], producing huge advances in RA treatment[1]. However, response to these therapies is heterogeneous, with about 30% of patients not responding well to biologics for reasons not yet fully elucidated[2]. In early or established RA, several studies have pointed out a lower response to anti-TNF drugs, particularly infliximab (IFX), in patients with a high body mass index (BMI)[3,4,5]. Moreover, other studies showed that obesity has also been associated with the increased incidence and a worse outcome of RA[6].

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TCZ is the first therapeutic agent targeting interleukin 6 (IL-6) to be effective in RA. It has been available and approved for treatment of patients with moderate to severe active RA who have had an inadequate response to 1 or more disease-modifying antirheumatic drugs (DMARD) and/or TNF antagonists[7]. As for IFX, the intravenous dose is adjusted to the weight. Wallenius, *et al* showed that mice without the gene encoding IL-6 (IL-6 knockout mice) developed obesity mainly because of an increase in subcutaneous fat mass[8]. Further, Younis, *et al* suggested that TCZ induced a significant weight and BMI increase among patients with RA compared to IFX[9]. Given the significant effect of IL-6 on the weight status of the subjects, our aim was to assess whether the response of patients with RA to treatment with TCZ depended on their BMI. Therefore, we examined the relationship between the BMI at baseline and the primary clinical response to TCZ in a retrospective cohort study.

MATERIALS AND METHODS

Study population. Our retrospective cohort included all patients treated with TCZ (8 mg/kg intravenously every 4 weeks) for RA between December 2009 and December 2012 in the rheumatology departments of 5 university hospitals in France (Besançon, Dijon, Grenoble, Montpellier, and Saint-Étienne). All patients fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) criteria for RA[10]. The clinical and biological data were collected retrospectively from medical records. According to the World Health Organization (WHO) criteria[11], normal weight was defined as a BMI < 25 kg/m^2, overweight as a BMI of 25–30 kg/m^2, and obesity as a BMI > 30 kg/m^2. TCZ doses could be adapted according to the recommendations of the European authorities[12]. The study was approved by the local ethics committee (Comité de

Protection des Personnes Sud Méditerranée IV, Montpellier, France) in accordance with the Helsinki Declaration.

Efficacy assessment. Response to TCZ treatment was evaluated using the EULAR criteria (good, moderate, or no response) at 6 months (primary endpoint). RA disease activity was assessed by the Disease Activity Score in 28 joints (DAS28), taking into account the erythrocyte sedimentation rate (ESR). We also evaluated the efficacy of TCZ using the proportion of patients in remission (DAS28-ESR < 2.6) and with low disease activity (LDA; DAS28-ESR < 3.2). We decided to evaluate the response at 6 months, as recently recommended[12]. This minimum period of evaluation allowed for a timely decision on the therapeutic efficacy and suitability of TCZ in our study.

Statistical analysis. A comprehensive description of the sample was achieved by giving the frequencies of different categories for qualitative variables. Since the distributions of quantitative variables were not always Gaussian, they were described using the mean and SD, and also the median and interquartile values. The distributions have been tested against the normal distribution using a Shapiro-Wilk test.

The characteristics of patients were compared between the 3 initial BMI groups (< 25 kg/m^2, 25–30 kg/m^2, and > 30 kg/m^2) using the chi-square test or the Fisher's exact test (if theoretical size < 5) for qualitative variables, and using ANOVA for quantitative variables. When the conditions of application of the latter test were not met (normal distribution, equal variances), Kruskal-Wallis test was used.

The relationship between the BMI and the response to treatment was studied by comparing the proportion of response to TCZ between the initial BMI groups using the chi-square test. To determine the predictors of response to TCZ according to the different definitions of this response (EULAR response, remission, LDA), we fitted univariate and multivariate logistic regressions. Multivariate logistic regressions were adjusted for age, sex, square root of disease duration, log of baseline C-reactive protein (CRP) and square root of ESR, presence of erosive lesions, rheumatoid factor, anticitrullinated protein antibodies, baseline DAS28 score, and concomitant therapy by DMARD (disease duration, baseline CRP, and ESR were transformed for the normalization of their distribution). We additionally used the relative change in swollen joint count (SJC) as another clinical outcome variable to evaluate the response to TCZ because it is not invariably influenced by TCZ therapy (unlike the EULAR response and DAS28). The relationship between the BMI and the response to treatment in terms of changes in the SJC was analyzed using bivariate and multivariate linear regression models before and after 6 months. Both models (bivariate and multivariate) were adjusted for SJC at baseline.

All statistical tests were 2-sided and with 0.05 significance level. Statistical analyses were performed using SAS software, version 9 (SAS Institute).

RESULTS

A total of 222 patients with RA were included. During the first 6-month period, 21 patients stopped the TCZ therapy: 9 for lack of response and 12 for intolerance. At 6 months, the EULAR response was not available for 11 of the 222 patients with RA. In accordance with the WHO definition[11], distribution of individuals having normal weight, overweight, and obesity was 58.5%, 26%, and 15.5%, respectively. Baseline characteristics of patients with RA are summarized in Table 1. We found no difference between BMI groups on all variables except for erosive status, which was significantly less frequent in obese patients with RA (p = 0.03). At baseline, mean weight and mean BMI status were, respectively, 66.6 kg (± 16.5) and 25.1 kg/m^2 (± 5.8). Treatment with TCZ was associated with a significant weight gain and BMI increase after 3 and 6 months (Table 2).

Efficacy of TCZ according to BMI. After 6 months of TCZ treatment, 55.3% of patients with RA were good responders (n = 105), 22.1% were moderate responders (n = 42), and 40.5% reached remission (n = 77). We found no differences in the response to TCZ or in rates of remission between the 3 BMI groups. Global EULAR response was reached in 86% of obese patients, 70% of overweight patients, and 80% of normal weight patients. The 6-month remission rates were 41%, 28%, and 46% in obese, overweight, and normal weight groups, respectively (Table 3). After multivariate analyses, BMI was not significantly associated with the EULAR response at 6 months (adjusted OR 0.45, 95% CI 0.16–1.24, p = 0.13 and OR 1.19, 95% CI 0.31–4.48, p = 0.78 for BMI 25–30 kg/m^2 and BMI > 30kg/m^2, respectively, compared to BMI < 25kg/m^2). Similar results were obtained when using other response criteria at 6 months (remission, LDA; Table 3). The changes of the SJC between baseline and 6 months did not significantly differ between the 3 groups of BMI in crude and adjusted analyses [adjusted mean (SE of the mean) = –3.13 (0.24), –2.8 (0.36), and –3.33 (0.43), respectively, for < 25 kg/m^2, 25–30 kg/m^2, and > 30 kg/m^2, p = 0.69]. Sensitivity analysis using the BMI as a 2-level categorical variable and as a quantitative variable did not show any significant association.

No correlation was found between BMI and DAS28. Essentially, when these variables were analyzed under their quantitative form (dot-plot analysis), there was no association between baseline BMI and the DAS28 score at 6 months or the changes of the DAS28 score between baseline and 6 months. The Spearman correlation coefficient values were 0.07 (p = 0.32) for BMI and –0.05 (p = 0.46) for DAS28 score.

DISCUSSION

In our study, we investigated, retrospectively, whether BMI could influence the response to TCZ in patients with RA. To our knowledge, this is the first report in patients with RA studying BMI and the response to TCZ therapy. Unlike what had been described with anti-TNF drugs, and especially IFX[3,4,5], the response to TCZ therapy does not seem lower in overweight and obese RA subjects. We also highlighted a significant weight gain and BMI increase during TCZ therapy similar to that found in Younis, *et al*[9].

In the BeSt study, Heimans, *et al* showed that overweight patients with RA had a higher risk of failure in obtaining LDA ≤ 2.4 [relative risk ratio (RR) 1.20, 95% CI 1.05–1.37] with the first therapeutic strategy (DMARD combination or IFX therapy)[4]. According to some authors[5], the lowest response observed in obese patients with RA treated with anti-TNF drugs could be related to the importance of inflammation in adipose tissue. Several studies suggested that adipose tissue is the site of a permanent inflammatory

Table 1. Baseline characteristics of patients with RA treated with TCZ according to different BMI groups. Values are % or median (IQR) unless otherwise specified.

Characteristics	Whole Population	BMI, n = 207*			p
		< 25 kg/m^2	25–30 kg/m^2	> 30 kg/m^2	
Patients, n (%)	222	121 (58.5)	54 (26.0)	32 (15.5)	
Age, yrs	56 (47–66)	55 (46–65)	58.5 (52–67)	56 (48–63.5)	0.29
Female sex	82.4	83.5	77.8	93.7	0.15
Disease duration, yrs	14 (8–22)	15 (8–23.5)	13 (8–24)	11 (8.5–19)	0.44
Erosive status	79.0	83.5	75.0	62.5	0.03
RF-positive	71.0	66.1	77.4	77.4	0.22
ACPA-positive	65.7	67.2	63.5	64.5	0.88
Previous biologics use, median (min–max)	2 (0–6)	3 (0–6)	2 (0–6)	2 (0–6)	0.08
Biologic-naive patients	13.1	11.6	18.5	9.4	0.38
Concomitant therapy					
MTX, n (%)	105 (47.3)	58 (47.9)	25 (46.3)	14 (43.7)	0.91
MTX dose, mg/wk	15 (10–15)	15 (10–15)	15 (10–15)	15 (12.5–17.5)	0.81
Steroid, n (%)	143 (64.7)	79 (65.8)	35 (64.8)	21 (65.6)	0.99
Steroid dose, mg/day	10 (5–10)	10 (5–15)	10 (5–10)	8 (5–10)	0.65
TCZ dose, mg/kg, median (min–max)	8 (4–8)	8 (4–8)	8 (8–8)	8 (8–8)	0.24
Disease activity measures					
TJC	8 (5–13.5)	7 (4–13)	10 (5–16)	8 (5.5–13)	0.31
SJC	4 (1–7)	4 (1–7)	4 (2–7)	3 (1–5)	0.25
ESR, mm/h	27 (11–44)	24 (10–39)	28 (11–44)	32 (21–57)	0.07
CRP, mg/l	8.0 (3–24.5)	6.3 (2.6–24.8)	8.0 (2.5–22.1)	11.2 (7.4–24.1)	0.11
DAS28-ESR, mean (SD)	5.09 (1.28)	5.04 (1.34)	5.14 (1.36)	5.22 (1.11)	0.75

* 15 patients had missing values for weight and/or height. RA: rheumatoid arthritis; TCZ: tocilizumab; BMI: body mass index; IQR: interquartile range; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; MTX: methotrexate; TJC: tender joint count; SJC: swollen joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints.

Table 2. Weight and BMI changes during 6-month TCZ therapy. Values are mean (SD) unless otherwise specified.

Characteristics	Baseline, n = 207*	Δ M3 – M0		Δ M6 – M0	
		n = 157	p	n = 157	p
Weight, kg	66.57 (16.5)	+0.65 (3.43)	0.001	+0.83 (3.32)	0.001
BMI, kg/m^2	25.1 (5.8)	+0.25 (1.28)	0.002	+0.34 (1.26)	< 0.001

* 15 patients had missing values for weight and/or height. BMI: body mass index; TCZ: tocilizumab; Δ M3 – M0: difference between 3 months and baseline; Δ M6 – M0: difference between 6 months and baseline.

process[13] that might explain the resistance of overweight patients with RA to targeting proinflammatory cytokines. In humans, serum levels of IL-6 are inversely correlated with the BMI and other metabolic variables such as insulin sensitivity[14,15]. Indeed, IL-6 blockade in animals induces obesity and insulin resistance[8]. IL-6 is one of the key mediators of the depleted fat reserves involved in cancer cachexia. Elevated serum IL-6 levels led to a decrease of lipoprotein lipase activity and may participate in the loss of body fat stores seen in cancer cachexia[16]. Some authors confirmed that healthy obese and non-obese patients presented lower concentration of inflammatory cytokines, such as IL-6, TNF-α, or CRP[17]. Although IL-6 plays a major role in inflammation and weight status, we did not demonstrate this therapy-resistant state with the inhibition of IL-6 by TCZ. The half-life of TCZ is concentration dependent, and the maximal concentration increases in proportion to increased dosages[18]. Because the TCZ dose is adjusted to body weight and the elimination is linear at high concentrations, one might expect serum TCZ concentrations to be higher in patients who are more obese. Thus, pharmacokinetics of TCZ may explain similar efficiency between lean and overweight subjects. On the other hand, it is known that in obese people, plasma cortisol levels are elevated, thus suggesting that obesity itself may induce high levels of cortisol, which could decrease the underlying inflammation[19]. Because TCZ therapy seems to induce a significant increase of weight gain[9], this effect may explain the difference in terms of the response between TCZ and anti-TNF drugs among obese patients with RA.

Limitations of our study include methodological issues related to its observational aspect. The retrospective

Table 3. Relationship between BMI and better response to TCZ at 6 months.

BMI	n (%)	p	OR (95% CI)	p	AOR (95% CI)	p
			Global EULAR Response			
< 25 kg/m^2	84 (80)	0.21	1		1	
25–30 kg/m^2	30 (70)		0.57 (0.25–1.29)	0.18	0.45 (0.16–1.24)	0.13
> 30 kg/m^2	25 (86)		1.56 (0.49–4.97)	0.45	1.19 (0.31–4.48)	0.78
> 25 kg/m^2	55 (76)	0.56	0.80 (0.39–1.66)	0.56	0.64 (0.26–1.60)	0.34
			Remission			
< 25 kg/m^2	48 (46)	0.13	1		1	
25–30 kg/m^2	12 (28)		0.46 (0.21–0.99)	0.04	0.41 (0.14–1.16)	0.09
> 30 kg/m^2	12 (41)		0.83 (0.36–1.92)	0.67	0.61 (0.21–1.70)	0.34
> 25 kg/m^2	24 (33)	0.09	0.59 (0.31–1.10)	0.10	0.50 (0.22–1.14)	0.09
			Low Disease Activity			
< 25 kg/m^2	66 (63)	0.17	1		1	
25–30 kg/m^2	22 (51)		0.61 (0.30–1.26)	0.18	0.59 (0.23–1.55)	0.28
> 30 kg/m^2	21 (72)		1.55 (0.62–3.83)	0.34	1.41 (0.46–4.36)	0.54
> 25 kg/m^2	43 (60)	0.67	0.87 (0.47–1.62)	0.67	0.84 (0.37–1.91)	0.68

AOR: OR adjusted for age, sex, square root of disease duration, presence of erosive lesions; rheumatoid factor, anticitrullinated peptide antibodies, erosive status, concomitant treatment with DMARD (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, or azathioprine); baseline DAS28; logarithm of baseline CRP; and square root of baseline ESR. BMI: body mass index; TCZ: tocilizumab; EULAR: European League Against Rheumatism; DMARD: disease-modifying antirheumatic drug; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

collection resulted in missing data. Moreover, BMI and DAS28 data were collected by multiple evaluators (nurse, physician) that could lead to a bias. However, our population sample had similar characteristics to the subjects included in the previous studies demonstrating a lower response to anti-TNF drugs in overweight patients with RA with about 15% of obese subjects[3,4,5]. We cannot exclude that the response of overweight patients with RA compared to leaner patients would have been different earlier (3 mos) or later (12 mos). However, we did not observe differences between BMI groups when we examined various modes of response at 3 months (data not shown). Even though the EULAR response was not significantly different in overweight or obese compared to normal weight patients with RA (OR 0.64, p = 0.34), our OR is similar to the RR (1.2) observed by Heimans, *et al*[4]. Thus, we cannot exclude that with a larger number of patients (by increasing the power of the analysis), we could have shown a lower response in overweight patients. Essentially, if we assumed an association between the BMI and the EULAR response with an RR 1.2 and 75% of the EULAR responders in the studied group, we estimated the power of our study to be 8.2%. We used the DAS28 score because it is the most widely used evaluation method in clinical practice even though another method of evaluation of the response excluding ESR or CRP [Clinical Disease Activity Index (CDAI)] would be more relevant with TCZ[20]. As a result of missing data, we were not able to calculate the CDAI or the Simplified Disease Activity Index, but we considered that the relative change in SJC would be a good alternative. We performed this additive analysis and did not find any other significant association between BMI and TCZ response.

We have shown no effect of the BMI on patient response to intravenous TCZ therapy in contrast to anti-TNF drugs. Because fat tissue may lead to a resistance to anti-TNF therapies compared to TCZ therapy, it could be of interest to examine whether the response would be different between each drug. Future research should assess these differences prospectively for better comparisons and should include a control group with an anti-TNF drug (such as IFX) in the study.

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