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Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis

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Abstract

Background Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by increased mortality associated with cardiometabolic disorders including dyslipidaemia, insulin resistance, and cachectic obesity. Tumour necrosis factor inhibitors and interleukin 6 receptor blocker licensed for the treatment of RA decrease inflammation and could thus improve cardiovascular risk, but their effects on body composition and metabolic profile need to be clarified. We investigated the effects of tocilizumab (TCZ), a humanized anti-interleukin 6 receptor antibody, on body composition and metabolic profile in patients treated for RA.

Methods Twenty-one active RA patients treated with TCZ were included in a 1 year open follow-up study. Waist circumference, body mass index, blood pressure, lipid profile, fasting glucose, insulin, serum levels of adipokines and pancreatic/gastrointestinal hormones, and body composition (dual-energy X-ray absorptiometry) were measured at baseline and 6 and 12 months of treatment. At baseline, RA patients were compared with 21 non-RA controls matched for age, sex, body mass index, and metabolic syndrome.

Results Compared with controls, body composition was altered in RA with a decrease in total and appendicular lean mass, whereas fat composition was not modified. Among RA patients, 28.6% had a skeletal muscle mass index below the cut-off point for sarcopaenia (4.8% of controls). After 1 year of treatment with TCZ, there was a significant weight gain without changes for fat mass. In contrast, an increase in lean mass was observed with a significant gain in appendicular lean mass and skeletal muscle mass index between 6 and 12 months. Distribution of the fat was modified with a decrease in trunk/peripheral fat ratio and an increase in subcutaneous adipose tissue. No changes for waist circumference, blood pressure, fasting glucose, and atherogenic index were observed.

Conclusions Despite weight gain during treatment with TCZ, no increase in fat but a modification in fat distribution was observed. In contrast, muscle gain suggests that blocking IL-6 might be efficient in treating sarcopaenia associated with RA.

Keywords Sarcopaenia; Cachexia; Rheumatoid arthritis; Tocilizumab; Metabolic change

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Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by progressive joint destruction, disability, and premature death with an increased cardiovascular mortality.[1] In addition to traditional cardiovascular risk factors, systemic inflammation and metabolic disorders including insulin resistance, dyslipidaemia, and cachectic obesity[2,3] contribute to this excess of cardiovascular risk and mortality. Among patients with RA, low body mass index (BMI) is associated

with cardiovascular death which could be related to cachexia-associated metabolic disorders.[4] Sarcopaenia is defined by both low muscle mass and muscle function (strength or performance) with a risk of physical disability, poor quality of life, and death.[5,6] During ageing and chronic diseases, decrease in lean mass is frequently associated with preserved or even increased body fat, notably ectopic fat in the muscles, regardless of changes in total body weight, thus defining sarcopaenic obesity. Sarcopaenic obesity implies a close link between adipose tissue and muscle. This new phenotype combines the risks arising from changes in muscle mass, limiting mobility and participating in the appearance of metabolic disorders, and from excess adiposity which generates significant adverse health effects (hypertension, dyslipidaemia, cardiovascular risk, and insulin resistance). The loss of muscle is associated with intramuscular or ectopic fat infiltration and increase in total and/or visceral adipose tissue responsible for the production of adipocytokines as well as lipotoxicity, mitochondrial dysfunction, oxidative stress, insulin resistance, and anabolic resistance. In turn, these disturbances exacerbate sarcopaenia, leading to a decrease in physical activity and resting energy expenditure in a self-contained loop. In RA, conventional disease-modifying antirheumatic drugs (DMARDs) and biologics targeting pro-inflammatory cytokines decrease inflammation and could thus improve cardiovascular risk. Cytokine inhibitors may also be a potential therapeutic approach for sarcopaenia as tumour necrosis factor (TNF) α and interleukin 6 (IL-6) are known to play a key role in muscle proteolysis, mitochondrial muscle dysfunction, and insulin resistance. However, body weight gain both with TNF inhibitors and IL-6 receptor (IL-6R) blocker has been reported in RA patients,[7–10] and its effect on body composition and cardiometabolic profile needs to be clarified.[11–14] With TNF blockers, two randomized trials in RA did not show any differences for body composition after 6 months and 1 year of treatment.[11,14] However, an increased in fat mass with preservation of muscle mass was observed with infliximab during long-term therapy (2 years).[14] The most commonly diagnosis tool used to assess body composition is the dual-energy X-ray absorptiometry (DXA). DXA allows distinguishing both lean and fat mass composition and identifying changes in the body fat distribution, android adiposity and visceral abdominal fat being the most associated with cardiometabolic disorders. To analyse the effect of IL-6 inhibition on body composition in patients with active RA treated with tocilizumab (TCZ), a humanized anti-IL-6R antibody directed to the IL-6Rα chain licensed for the treatment of RA, we conducted a 1 year open follow-up study. Changes in lean and fat mass were assessed at 6 and 12 months of treatment with DXA and compared at baseline to 21 non-RA matched controls. In addition, metabolic profile, serum levels of adipokines, and pancreatic/gastrointestinal hormones were investigated.

Methods

Patients

Twenty-one consecutive patients with active RA and starting new treatment with TCZ were included between June 2011 and January 2013 in an open, prospective 1 year follow-up study. The patients fulfilled the 2010 RA classification criteria[15] and had active disease as defined by disease activity score in 28 joints (DAS28) >3.2. The study was approved by the local ethics committee (Institutional Review Boards: 00008526). All patients received verbal and written information and signed a consent form prior to inclusion. Longitudinal data were available for 21 RA patients at baseline, 15 patients at 6 months, and 11 at 1 year of follow-up.

Controls

For baseline references, data were obtained from 21 non-RA controls recruited in the Reverse Metabolic Syndrome by Lifestyle and Various Exercises trial between May 2009 and October 2011[16] and matched with RA patients for age, sex, BMI, and criteria of metabolic syndrome. Briefly, patients with metabolic syndrome had a sedentary lifestyle, stable body weight, and medication over the previous 6 months. They had no chronic diseases except those defining metabolic syndrome, no medications altering body weight, and no restricted diet in the previous year. Healthy participants had none of the defined criteria of metabolic syndrome, no chronic disease, no routine medication, unchanged lifestyle over the previous 12 months, and less than 3 h per week of physical activity. For matching, BMI was categorized as <25 Kg/m^2, 25–30 Kg/m^2, and >30 Kg/m^2. Metabolic syndrome was defined according the new WHO criteria.[17]

Measurements

Patient disease assessment

Demographic, disease, and clinical characteristics were assessed at baseline and 6 and 12 months post treatment. Disease duration, smoking, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, DAS28 using erythrocyte sedimentation rate, European League Against Rheumatism (EULAR) response, erosion on radiographs, current and past use of glucocorticoids, and biologic and non-biologic DMARDs were recorded.

Body composition

All subjects underwent total body DXA scanning (HOLOGIC Discovery A S/N 85701). Fat, lean, and bone masses for the

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total body and per region (arms, legs, and trunk) were measured and analysed by using the manufacturer's validated software (version 4.02 HOLOGIC APEX). Daily quality control and calibration procedures were performed by using the manufacturer's standard.

Body fat percentage was calculated as the proportion of total fat mass to total mass. Appendicular fat and lean masses were computed as the sum of the tissue compartment (fat or lean) of both arms and legs. Skeletal muscle mass index (SMI) was calculated as appendicular lean mass divided by height $(m)^2$, fat mass index as total fat mass divided by height $(m)^2$, and fat-free mass index as total body mass without total fat mass divided by height $(m)^2$. The trunk-peripheral fat ratio, a measure of 'android' fat, was calculated by using fat of the body trunk divided by the peripheral (legs and arms) fat. Separation of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) was performed by two blinded readers (SMG and CG) inside a region of interest by using a new software developed on DXA with a validated method.[18,19] Lin's concordance correlation coefficient for the inter-reader concordance was 0.96 for VAT and 0.99 for SAT. The ratio of VAT area/SAT area was calculated. An SMI lower than two SDs below the mean SMI of young male and female reference groups was defined as the gender-specific cut point for sarcopaenia (Baumgartner's criteria: men 7.26 kg/m^2, women 5.5 kg/m^2).[5]

Cardiometabolic profile

Weight, height, waist circumferences, blood pressure, and information on cholesterol-lowering, antihypertensive, antidiabetic drugs were obtained from all patients. BMI was calculated as weight (kg) divided by height (m^2). Fasting glucose and lipid profile [total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides] were measured. The atherogenic index (total cholesterol/HDL cholesterol) was then calculated.

Serum levels of adipokines and pancreatic/gastrointestinal hormones were available for 15 patients at baseline and for 10 patients after 6 months of treatment. Adiponectin, leptin, chemerin, visfatin, and resistin were assayed by enzyme-linked immunosorbent assay with commercial kits (Biovendor, Brno, Czech Republic). Insulin, ghrelin, amylin, C peptide, gastric inhibitory polypeptide, glucagon-like peptide-1, pancreatic polypeptide, and peptide tyrosine tyrosine were measured with luminex bead-based multiplex assay (Milliplex kit, Merck Millipore KGaA, Darmstadt, Germany). Insulin resistance was assessed by using the homeostatic model homeostatic model assessment for insulin resistance [(insulin [mU/L] × glucose [mmoles/L]) ÷ 22.5][20] for 14 patients at baseline and 9 patients at 6 months, after exclusion of one patient with uncontrolled hyperglycaemia. Data were not available at 12 months.

Statistical analysis

The sample size was determined according to simulations on effect size. For a two-sided type error of 5%, a statistical power equal to 90%, and a correlation coefficient of 0.50 (paired context), $n = 13$ patients (at M6) were necessary to highlight an effect size equals 1. For the same assumptions, $n = 10$ (at M12) allowed a statistical power equals 80%. Statistical analysis was performed by using Stata 13 software (StataCorp LP, College Station, TX, US). The tests were two-sided, with a type I error set at $\alpha = 0.05$. The results were presented as mean (±SD) or median (interquartile range) for continuous data and as the number of patients and associated percentages for categorical parameters. Comparisons between the independent groups were performed by using the chi-squared or Fisher's exact tests for categorical variables and Student's *t*-test or Mann–Whitney test for quantitative parameters. The relationship between quantitative outcomes was studied with correlation coefficients. Considering the several multiple comparisons, an inflation of the type I error was applied (Sidak's correction). Repeated data were compared by using mixed models to take into account within-subject and between-subject variabilities (patient as random effect). All the individual *P*-values were reported without systematic mathematical correction for distinct tests.[21] Sensitivity analyses investigated the impact of the missing data on the results. In order to assess the issue of missing data, the estimation methods developed by Verbeke and Molenberg[22] were considered. A particular focus was given to the magnitude of difference and to the clinical relevance.[23] Available-case analysis on completers (longitudinal analysis for the 11 patients who had data at baseline, 6 months, and 1 year) and comparison of baseline characteristics between the 11 patients which have completed the study at 1 year (completers) and the 10 patients for which data were missing (non-completers) were performed. All statistical analyses were performed by the biostatistics unit (DRCI) of the University Hospital of Clermont-Ferrand (B. Pereira, PhD Biostatistics).

Results

Baseline characteristics of rheumatoid arthritis patients and matched non-rheumatoid arthritis controls

The baseline characteristics of 21 RA patients and 21 matched non-RA controls are shown in *Table* 1. Patients with RA received more cholesterol-lowering drug, and the atherogenic index was lower. During the follow-up, the proportion of RA patients with cholesterol-lowering drug did not significantly change from baseline (73% at 6 and 12 months). Fourteen patients in the RA group were currently receiving steroids, while none in the control group. The number of

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Table 1 Baseline characteristics of the 21 patients with rheumatoid arthritis treated with tocilizumab and 21 controls matched for age, sex, body mass index, and criteria of metabolic syndrome [mean ± SD or number (%)]

	RA (n = 21)	Controls (n = 21)
Age, years	57.8 ± 10.5	57.8 ± 5.4
Gender, female	16/21 (76)	16/21 (76)
Body weight, Kg	61.8 ± 19.3	68.4 ± 15.0
BMI, Kg/m^2	23.6 ± 6.7	24.6 ± 5.4
Waist circumference, cm	85.4 ± 13.6	83.6 ± 11.7
Metabolic syndrome	6/21 (28.5)	6/21 (28.5)
HOMA-IR [(insulin × glucose) / 22.5]	2.35 ± 1.3	2.36 ± 1.3
Triglycerides, g/L	0.99 ± 0.45	1.16 ± 0.64
Total cholesterol, g/L	2.05 ± 0.43	2.25 ± 0.29
LDL cholesterol, g/L	1.26 ± 0.32	1.42 ± 0.25
HDL cholesterol, g/L	0.66 ± 0.20	0.6 ± 0.18
Total/HDL cholesterol	3.30 ± 1.02	4.07 ± 1.29*
Cholesterol-lowering drug therapy	11/21 (52.4)	3/21 (14.3)**
Antihypertensive drug	6/21 (28.5)	4/21 (19)
Antidiabetic drug	1/21 (5)	2/21 (9.5)
Disease duration; median [IQR]	8.5 [1.7–21.5]	—
Rheumatoid factor positivity	14/21 (67)	—
Anti-cyclic citrullinated peptide antibodies	18/21 (86)	—
Radiographic erosions	13/21 (62)	—
DAS28	4.94 ± 1.25	—
C reactive protein level, mg/L median [IQR]	4.5 [2.9–31.1]	
EULAR response M6/M12		
No	4/2	—
Good–moderate	10/9	—
Smoking	10/21 (48)	NR
Concomitant DMARD	19/21 (90)	—
Current steroids	14/21 (67)	0/21
Mean steroid dosage (prednisone mg/d)	4.12 ± 3.35	—
At least one previous biologic	18/21 (86)	—

BMI, body mass index; DAS28, disease activity score in 28 joints; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; IQR, interquartile; LDL, low-density lipoprotein; NR, not relevant; RA, rheumatoid arthritis.
*$P < 0.05$.
**$P < 0.01$.

RA patients on steroids and the mean steroid dosage did not change during the follow-up. Eighteen RA patients (86%) had previously received at least one biologic. The mean baseline DAS28 decreased significantly at 6 and 12 months (2.92 ± 0.8 and 2.8 ± 1.5, respectively, $P < 0.001$).

Comparison of rheumatoid arthritis patient body composition with matched non-rheumatoid arthritis controls

The baseline body composition of RA patients and controls is shown in *Table* 2. Compared with controls, RA patients had significantly lower total and appendicular lean mass at baseline. The SMI was not significantly decreased because the height was higher in non-RA controls (1.68 m vs 1.61 m, P = 0.02). In the RA group, six patients (28.6%) had an SMI value below the cut-off point for sarcopaenia, whereas only one control (4.8%) had sarcopaenia defined in this way (P = 0.04). Measures of fat mass and distribution of the fat did not differ significantly between RA and controls. Among the six RA patients with sarcopaenia as defined by an SMI value below the gender-specific cut point for sarcopaenia (Baumgartner's criteria), four had also a BMI below 20 and would therefore be considered cachectic. One other patient had a sarcopaenic obesity defined on DXA by the association of an SMI below the gender-specific cut point for sarcopaenia and a body fat percentage above 27% for men and 38% for women.[24] In non-sarcopaenic RA patients, four had overfat defined on DXA criteria[24] and two had a BMI <20 without sarcopaenia.

Table 2 Baseline body composition of rheumatoid arthritis patients treated with tocilizumab and controls [mean ± SD or number (%)]

	RA (n = 21)	Controls (n = 21)
Total lean mass, Kg	42.1 ± 11.1*	47.5 ± 8.7
Appendicular lean mass, Kg	17.7 ± 5.4*	20.1 ± 3.9
Fat-free mass index (FFMI), Kg/m^2	16.7 ± 3.0	17.6 ± 2.6
Skeletal muscle mass index (SMI), Kg/m^2	6.7 ± 1.4	7.1 ± 1
SMI cut-off points for sarcopaenia (women ≤ 5.5 Kg/m^2; men ≤ 7.26 Kg/m^2)	6/21 (28.6%)*	1/21 (4.8%)
Total fat mass, Kg	19.5 ± 12.3	19.7 ± 9.6
Body fat percentage, %	29.4 ± 9.8	27.5 ± 8.0
Fat mass index (FMI), Kg/m^2	7.5 ± 4.8	7.0 ± 3.4
Trunk/peripheral fat ratio	0.77 ± 0.22	0.89 ± 0.25
Visceral adipose tissue (VAT), cm^2	74.3 ± 43.1	108.9 ± 69.1
Subcutaneous adipose tissue (SAT), cm^2	241.3 ± 173.3	256.6 ± 123.7
VAT/SAT ratio	0.36 ± 0.21	0.43 ± 0.21

FFMI = lean mass + bone mineral content / height^2; FMI = fat mass / height^2; SMI = appendicular (4 limbs) lean mass / height^2.
*$P < 0.05$.

Body composition changes of rheumatoid arthritis patients during treatment with tocilizumab

Body composition changes at 6 and 12 months of follow-up are presented in *Table* 3. After 1 year of treatment with TCZ, we observed a significant weight and BMI gain without changes for fat composition. In contrast, total lean mass and fat free mass index increased at 1 year. There was a significant gain in appendicular lean mass at 12 months and both at 6 and 12 months for the SMI with a significant change between 6 and 12 months (P = 0.017).

Moreover, this increase in lean mass was associated with modification of the fat distribution. A decrease in trunk/peripheral fat ratio and an increase in SAT were observed at 1 year, whereas VAT did not change. The VAT/SAT ratio decreased at 1 year, but the difference was borderline significant (P = 0.07).

Disease characteristics at baseline (age, duration, smoking, DAS28, radiographic erosion, past use of biologics or steroids,

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Table 3 Body composition changes of patients with active rheumatoid arthritis treated with tocilizumab during 1 year follow-up with tocilizumab treatment [mean ± SD or number (%)]

	Baseline	6 months	1 year
Body weight, Kg	61.8 ± 19.3	60.9 ± 15.6	63.7 ± 16.1**
BMI, Kg/m2	23.6 ± 6.7	23.6 ± 5.2	24.8 ± 5.9**
Waist circumference, cm	85.4 ± 13.6	88.9 ± 14.6	91.7 ± 14.0
Total lean mass, Kg	42.1 ± 11.1	41.9 ± 11.8	43.2 ± 11.3*
Appendicular lean mass, Kg	17.7 ± 5.4	17.9 ± 5.3	18.7 ± 5.6***
Skeletal muscle mass index (SMI), Kg/m^2	6.7 ± 1.4	6.9 ± 1.3*	7.2 ± 1.5***
Fat-free mass index (FFMI), Kg/m^2	16.7 ± 3	16.9 ± 3	17.4 ± 3*
Total fat mass, Kg	19.5 ± 12.3	18.8 ± 8.6	19.5 ± 9.5
Body fat percentage, %	29.4 ± 9.8	29.6 ± 9.2	29.4 ± 8.8
Fat mass index (FMI), Kg/m^2	7.5 ± 4.8	7.4 ± 3.8	7.8 ± 4.3
Trunk/peripheral fat ratio	0.77 ± 0.22	0.75 ± 0.16	0.70 ± 0.17***
Visceral adipose tissue (VAT), cm^2	74.3 ± 43.1	76.6 ± 43.4	71.5 ± 33.7
Subcutaneous adipose tissue (SAT), cm^2	241.3 ± 173.3	233.1 ± 134.3	263.9 ± 154.3**
VAT/SAT ratio	0.36 ± 0.21	0.34 ± 0.17	0.31 ± 0.19

FFMI = Lean mass + bone mineral content / height^2; FMI = fat mass / height^2; SMI = appendicular (4 limbs) lean mass / height^2; trunk/peripheral fat ratio = trunk/legs and arms fat mass.
***$P < 0.001$.
**$P < 0.01$.
*$P < 0.05$.

and steroid dose) or EULAR response were not predictive of changes in lean mass. No significant correlation between baseline lean mass and EULAR response was observed. However, patients with a good–moderate EULAR response were different in baseline fat composition compared with patients without response. Baseline appendicular fat mass was higher in patients with good–moderate EULAR response at 6 months (9.8 ± 3.6 vs 6.5 ± 1.9 Kg, $P = 0.03$). Percentage of fat (32 ± 8% vs 17 ± 5%, $P = 0.03$), appendicular fat mass (10.8 ± 4.3 vs 5.4 ± 0.2 Kg, $P = 0.03$), and fat mass index (8.45 ± 4.2 vs 3.7 ± 0.42, $P = 0.03$) were increased at baseline in patients with a 12 month good–moderate EULAR response. This

Table 4 Cardiovascular and metabolic changes in patients with active rheumatoid arthritis receiving tocilizumab during 1 year follow-up [mean ± SD or number (%)]

	Baseline	6 months	1 year
Systolic blood pressure, mmHg	123 ± 13	126 ± 14	125 ± 19
Systolic blood pressure ≥ 140 mmHg	3/20 (15)	3/15 (20)	4/10 (40)
Diastolic blood pressure, mmHg	72 ± 10	74 ± 10	71 ± 11
Diastolic blood pressure ≥ 90 mmHg	1/20 (5)	2/15 (13.3)	1/10 (10)
Total cholesterol, g/L	2.05 ± 0.43	2.24 ± 0.38*	1.86 ± 0.47
LDL cholesterol, g/L	1.26 ± 0.32	1.33 ± 0.39	1.01 ± 0.38
HDL cholesterol, g/L	0.66 ± 0.20	0.73 ± 0.23*	0.68 ± 0.21
Total/HDL cholesterol	3.30 ± 1.02	3.33 ± 1.23	2.87 ± 0.76
Fasting glucose, g/L	0.79 ± 0.16	0.97 ± 0.55	1.02 ± 0.37
Fasting glucose ≥ 1 g/L	3/21 (14.3)	3/13 (23.1)	2/10 (20)
Triglycerides, g/L	0.99 ± 0.45	0.99 ± 0.40	0.90 ± 0.35
C reactive protein level, mg/L median [IQR]	4.5 [2.9–31.1]	2.9 [1–2.9]**	1 [1–2.9]***
HOMA-IR[a]	2.1 ± 1.1	3.9 ± 5.1	NA
Adipokines			
Adiponectin (μg/L)	20.2 ± 6.7	22.9 ± 5.1	
Leptin (ng/L)	15.5 ± 17.2	13.3 ± 17*	
Chemerin (ng/L)	52.1 ± 61.7	53.1 ± 69.7	
Resistin (ng/L)	4.2 ± 1.4	4.1 ± 1.5	
Visfatin (ng/L)	1.9 ± 2.9	1.7 ± 2	
Ghrelin (active, pg/mL)	30.6 ± 23.3	23.0 ± 21.2	
Amylin (pg/mL)	14.9 ± 7.7	18.3 ± 11.4	
C peptide (pg/mL)	736 ± 359	934 ± 619	
GIP (pg/mL)	54 ± 30	161 ± 192*	
GLP-1 (active, pg/mL)	23.1 ± 31	20.3 ± 32	
Pancreatic polypeptide (pg/mL)	120.6 ± 94.9	237.8 ± 260.7	
PYY (pg/mL)	117.5 ± 126.0	143.3 ± 149.7	

GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; IQR, interquartile; LDL, low-density lipoprotein; PYY, peptide tyrosine tyrosine.
[a]One patient with an extreme value was excluded from analyses.
***$P < 0.001$.
**$P < 0.01$.
*$P < 0.05$.

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correlation between baseline fat mass and EULAR response may suggest that patients with less severe and refractory disease had more fat mass and less cachexia.

Cardiometabolic changes of rheumatoid arthritis patients during treatment with tocilizumab

The results for cardiovascular and metabolic profiles are shown in *Table* 4. During treatment with TCZ, no changes for waist circumference, blood pressure, fasting glucose, and triglycerides were observed. Total cholesterol and HDLc increased significantly at 6 months of follow-up without modification of the atherogenic index. However, compared with 6 months of follow-up, total and LDL cholesterol levels as well as atherogenic index significantly decreased after 1 year of treatment ($P = 0.007$, $P = 0.01$, and $P = 0.05$, respectively). Insulin resistance was not modified at 6 months of follow-up. Among adipokines, only serum levels of leptin were significantly decreased at 6 months. The leptin/adiponectin ratio used as a biomarker of cardiovascular risk[25] decreased but not significantly (0.76 ± 0.88 vs 0.58 ± 0.73, $P = 0.08$). The gastric inhibitory polypeptide, an incretin secreted by gut in response to feeding and involved in insulin secretion, was increased after 6 months of treatment, whereas the second incretin glucagon-like peptide-1 was not modified.

Sensitivity analysis

A comparison between the 11 patients who have completed the study at 1 year and the 10 patients for which data were missing did not show any significant differences for demographic, disease, and clinical characteristics (*Table* S1). Among the 10 non-completers, the four patients for which the data were missing between 6 and 12 months consisted of three good–moderate EULAR responders and one non-responder at 6 months. The significant gain in lean mass was confirmed by using available-case analysis in RA patients treated with TCZ during 1 year of follow-up (*Table* S2). Compared with the full data analysis, significant differences for the gain in weight and lean mass persisted for fat-free mass index, total lean mass, appendicular lean mass, and SMI. Body fat percentage decreased between 6 and 12 months. Consistent with the full analysis, a redistribution of the fat towards peripheral and subcutaneous compartments was noted after 1 year of follow-up.

Discussion

Our results confirm a decrease in muscle mass in RA patients compared with controls contrasting with normal fat mass. We observed that almost one-third of RA patients had a muscle mass below the cut-off value for sarcopaenia defined by the European Working Group on Sarcopenia in Older People (EWGSOP),[5] contrasting with normal fat mass. Moreover, for the majority of sarcopaenic patients, the decrease in lean mass was associated with a low BMI (<20) supporting the evidence for rheumatoid cachexia in these patients with active and refractory disease. Rheumatoid cachexia, a complex metabolic syndrome, which associates sarcopaenia with or without loss of fat mass, underlying illness, inflammation, insulin resistance, anorexia, and increased breakdown of muscle proteins, was described almost 100 years ago, and a number of studies reported abnormal body composition in RA patients.[26] However, rheumatoid cachexia is under-recognized in clinical practice and few recent data are available regarding the body composition of RA patients assessed with DXA, the most useful and validated method, compared with controls.[27,28] The frequency of rheumatoid cachexia in the literature depends upon the definition of cachexia and/or sarcopaenia, the methods for assessing muscle mass, and the cut-off values. Although the definition of sarcopaenia should include both low muscle mass and low muscle function,[5] a combination of the two criteria was not reported in rheumatoid cachexia or sarcopaenia studies. Cachexia was diagnosed in two-third of patients by using anthropometric method,[29] whereas Giles *et al*. observed rates of sarcopaenia similar to ours (21.4% in women with RA and 33.3% in men with RA) by using alternative SMI cut points for sarcopaenia without muscle function assessment.[28] The mechanisms responsible for muscle loss have yet to be elucidated but could involve disease activity, the reduced mobility, and corticosteroid treatment.[6,30,31] In turn, altered body composition is likely to impact health and causes a cascade of cardiometabolic abnormalities.[32,33]

This first study of the impact of IL-6 inhibition on body composition in RA shows a gain in weight likely to be related to a significant increase in muscle mass as no change for fat mass was detected. To date, no specific therapeutic strategy for rheumatoid cachexia has been defined. Available therapeutic methods include increasing physical activity with high-intensity resistance training[34] and dietary treatment, although most RA patients do not have deficiencies in protein or energy intake, resulting in a possible increase in fat mass with cardiometabolic consequences. Clinical management should then include the tight control of systemic inflammation and RA activity. While cancer cachexia could be improved with TCZ,[35,36] the effect of DMARDs on body composition in RA and on metabolic profile needs to be further investigated to prove their efficacy and safety.[11–14] Weight and fat gain reported in many studies with TNF blockers or TCZ raises the question of their cardiovascular and metabolic tolerance.[7–10,12,14] In our study, the cardiometabolic safety profile under treatment appears to be favourable with a fat redistribution towards peripheral and subcutaneous fat. The exact function of each

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adipokine in the context of chronic inflammation remains uncertain.[37] However, many authors consider leptin, resistin, and visfatin as pro-inflammatory mediators, whereas adiponectin can have pro-inflammatory or anti-inflammatory properties depending on the isoform studied.[38,39] Leptin, a key regulator of appetite, by inducing the expression of anorexigenic factors and inhibiting the production of orexigenic peptides, stimulates the production of TNFα, IL-6, and IL-12. In turn, TNFα and IL1 up-regulate leptin production.[38] While elevated serum and synovial fluid leptin levels were reported in RA,[38] conventional DMARDs and TNF blockers did not modify the levels of leptin.[38] Our results showing a significant decrease after 6 months on TCZ treatment might suggest a pro-inflammatory IL-6 mediated effect of the leptin.

Several limitations to our study should be noted. Muscle function, a key indicator of sarcopaenia using the EWGSOP recommendation,[5] was not assessed in our study. However, a recent meta-analysis in a Brazilian population did not find significant difference for the prevalence of sarcopaenia using muscle mass and function criteria (EWGSOP) or muscle mass alone (Baumgartner's criteria).[40] The low number of patients and the missing data, though taken into account in the statistic models, could be insufficient to exclude an effect of TCZ on cardiometabolic profile. Moreover, the lack of control arm does not allow concluding for a specific effect of IL-6 inhibition on body composition. However, despite the low number of patients, we were able to observe a significant change for all the parameters of lean body mass with TCZ treatment. The muscle gain observed at 1 year suggests that blocking IL-6 might be efficient in reversing muscle loss associated with RA. These preliminary results need to be confirmed in larger population and in randomized controlled study to compare with conventional DMARDs and other biologics.

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The authors certify that they comply with the ethical guidelines for publishing in the *Journal of Cachexia, Sarcopenia and Muscle*: update 2015.[41]

The study was approved by the local ethics committee (Institutional Review Boards: 00008526). All patients received verbal and written information and signed a consent form prior to inclusion.

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Online supplementary material

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Comparison between one year treatment completers and non-completers among RA patients

Table S2. Available-case analysis of RA patients treated with tocilizumab during 1 year follow-up with TCZ treatment. [mean ± SD or number (%)]

Conflict of interest

Bruno Pereira, Fréderic Dutheil, Charlotte Giraud, Daniel Courteix, Vincent Sapin, Thomas Frayssac, and Sandrine Malochet-Guinamand declare that they have no conflict of interest.

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