Rheumatology International (2019) 39:1181–1189
https://doi.org/10.1007/s00296-019-04303-x

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Dynamics of body mass index and visceral adiposity index in patients with rheumatoid arthritis treated with tofacitinib

Diana S. Novikova[1] · Helen V. Udachkina[1] · Eugenia I. Markelova[1] · Irina G. Kirillova[1] · Anna S. Misiyuk[1] · Natalia V. Demidova[1] · Tatiana V. Popkova[1]

Received: 20 February 2019 / Accepted: 9 April 2019 / Published online: 3 May 2019

Abstract

The increase in cardiovascular risk in patients with rheumatoid arthritis (RA) compared with the general population is due to the combined effect of traditional risk factors for cardiovascular diseases, metabolic disorders, systemic inflammation, and side effects of antirheumatic drugs. Tofacitinib (TOFA) is an oral reversible inhibitor of janus kinases for the treatment of RA with proven efficacy and good tolerability, but its effects on body weight and metabolic profile need to be clarified. We investigated the effects of TOFA on body mass index (BMI) and visceral adiposity index (VAI) in RA patients. Thirty-one consecutive patients with active RA and starting new treatment with TOFA were included in a prospective 1 year follow-up observational study of cardiovascular effects of TOFA treatment. Weight, height, waist circumference, BMI, blood pressure, lipid profile, fasting glucose and VAI were measured at baseline and 12 months of treatment. Median weight gain was 3 kg (4.2%) after 1 year of TOFA. 23 (74%) patients suffered from a weight gain, and 6 (26%) out of them from a weight increment of 10% or more. Patients with lower BMI ($p = 0.024$) and higher baseline DAS28 [ESR] ($p = 0.017$) have the risk of an increase in BMI > 5% during TOFA treatment in a multivariate analysis. A decrease in VAI after 12 months was recorded. Weight increment and improvement of VAI are frequent on TOFA treatment. BMI dynamics associated with higher disease activity at baseline and lower baseline BMI.

Keywords Rheumatoid arthritis · Tofacitinib · Body mass index · Visceral adiposity index

Introduction

The increase in cardiovascular risk (CVR) in patients with rheumatoid arthritis (RA) compared with the general population is due to the combined effect of traditional risk factors (TRF) for cardiovascular diseases (CVD), metabolic disorders, systemic inflammation and side effects of antirheumatic drugs [1]. The contribution of metabolic disorders, especially obesity, to the development of RA and its outcomes has been intensively studied [2, 3]. Visceral adipose tissue (VAT) has an auto-, para- and endocrine function, producing biologically active substances that regulate the metabolic processes and immune reactions involved in inflammation, development of insulin resistance (IR), dyslipidemia (DLP), arterial hypertension (AH) and pathogenesis of cardiovascular and autoimmune diseases [4]. The risk of developing RA in patients with obesity increases 1.3–3.7 times [2, 3, 5]. A high prevalence of obesity was noted in patients with RA, especially women, regardless of the disease duration [6, 7]. Data on the effects of obesity on

✉ Diana S. Novikova
diananovikova75@yandex.ru

Helen V. Udachkina
helen.udachkina@gmail.com

Eugenia I. Markelova
evgenia-i.m@yandex.ru

Irina G. Kirillova
dr.i.kirillova@yandex.ru

Anna S. Misiyuk
anna.misiyuk@mail.ru

Natalia V. Demidova
natasha-demidova@mail.ru

Tatiana V. Popkova
popkovatv@mail.ru

[1] Department of Systemic Rheumatic Diseases, V.A. Nasonova Research Institute of Rheumatology, Kashirskoe shosse 34A, Moscow 155522, Russian Federation

the course of RA and CVR are contradictory. On the one hand, obesity is associated with higher RA disease activity, decreased efficacy of antirheumatic drugs, low quality of life and high frequency of comorbid conditions, including CVD [8–11]. On the other hand, the protective effect of obesity on the destruction of small joints and X-ray progression of RA has been demonstrated [11–13]. In RA, obesity does not lead to an increase in mortality or is even associated with the mortality decrease, while being underweight is associated with the highest risk of mortality, the so-called "obesity paradox" [14–17]. This is due to the fact that "rheumatoid cachexia" and/or rapid weight loss reflects the systemic process of inflammation and the severity of RA, which are key factors in the development of cardiovascular and overall mortality [18–20]. In patients with RA, body mass index (BMI) is rarely below normal, since a decrease in muscle mass is compensated by an increase in adipose tissue ("sarcopenic obesity") [21, 22]. This obesity phenotype combines the risks of reducing muscle mass (limited mobility, metabolic disorders) and an increase in adipose tissue (AH, DLP, IR, CVR).

Despite the introduction in clinical practice of modern methods of quantitative assessment of the mass of VAT in the human body (computer and magnetic resonance imaging), the anthropometric method has not lost its scientific and practical significance. This method is based on the determination of surrogate indicators of visceral obesity—BMI, waist/hip circumference (WC/HC) and visceral adiposity index (VAI). BMI is incorrectly regarded as an indicator reflecting the content of adipose tissue in the body [23]. Waist circumference is an acceptable indicator for assessing the distribution of adipose tissue, but it is not able to separate subcutaneous and visceral accumulation of adipose tissue. VAI is a mathematical model depending on the BMI, WC, cholesterol, high-density lipoproteins cholesterol (HDL-C), triglycerides (TG) and gender [24]. VAI is a marker of VAT dysfunction, independently correlating with all components of metabolic syndrome and CVR in the general population [25].

Despite the encouraging trend in the decline of CVR on active treatment of RA [26, 27], recently published data from a large population-based cohort study have shown that the elevated risk of acute coronary syndrome in RA remains higher compared with the general population [28]. Achieving RA remission may contribute to a reduction in the severity of "rheumatoid cachexia"; however, weight and adipose tissue gain was previously observed during therapy with TNF-α inhibitors (iTNF-α) and an IL-6 receptor inhibitor [29–33]. Tofacitinib (TOFA) is an oral reversible inhibitor of janus kinases (JAK) for the treatment of RA with proven efficacy and good tolerability [34, 35]. The mechanism of action of TOFA is the reversible competitive inhibition of the ATP-binding sites of JAK1, JAK2 and JAK3 and, to a minimum, TYK2. TOFA modulates the transmission of intracellular signals of key pro-inflammatory cytokines. According to clinical studies of phase 3 and the phase of prolonged follow-up, the frequency of cardiovascular events when using the drug is comparable to that when using biologic disease-modifying antirheumatic drugs (bDMARDs) [35, 36]. The increase in total cholesterol and cholesterol of low-density lipoproteins (LDL-C) due to a decrease in catabolism of cholesterol ester and an increase of anti-atherogenic properties of HDL-C is observed on TOFA treatment [37, 38]. Tofacitinib reduced RA disease activity and limited vascular damage despite up-regulating cholesterol in patients with an active RA [39].

Objective To assess the dynamics of BMI and VAI in RA patients during treatment with TOFA during 12 months of follow-up.

Subjects and methods

Study design

The present study is a prospective 1 year follow-up observational study of cardiovascular effects of TOFA treatment. This study was the part of scientific research of V.A. Nasonova Research Institute of Rheumatology «Optimization of diagnostic and treatment methods of cardiovascular disease in rheumatic diseases», № state registration 01200907561. The trial was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participating patients gave their written informed consent to participate. The study was approved by the local ethics committee in V.A. Nasonova Research Institute of Rheumatology (protocol #4, 11th of December 2014).

Inclusion and exclusion criteria

From February June 2015 to December 2016, consecutive patients older than 18 years, with a clinical diagnosis of RA fulfilling the 2010 classification criteria for RA [40], for whom new treatment with TOFA was indicated according to their rheumatologist, were included. They were non-responders to at least one DMARD (insufficient effect of previous MT therapy in an adequate (at least 15 mg/week) or maximum tolerated dose for at least 3–4 months; or MT intolerance and insufficient effect of leflunomide at a dose of 20 mg per day for at least 3–4 months). Additional inclusion criteria were active disease as defined by disease activity score in 28 joints (DAS28) > 3.2, negative pregnancy test in women of childbearing age and use of contraception by men and women of childbearing age during participation in the programme.

Patients were excluded if they had been treated with anti-TNF drugs in the last 3 months prior to inclusion, received intravenous corticosteroids within 14 days before inclusion and if they had ongoing treatment with oral moderate- to high-dose corticosteroids (equivalent to > 10 mg of prednisolone daily) or had completed such treatment less than 15 days before inclusion. Patients were excluded if they had a history of infections requiring treatment within 2 weeks, had severe, progressive or uncontrolled renal, hepatic, haematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological or cerebral disease; history of cancer in the previous 10 years; HIV, hepatitis B or C, inadequately treated or undocumented treatment of tuberculosis; had more than one episode of herpes zoster, one episode of disseminated herpes zoster or herpes simplex; clinically significant laboratory abnormalities (leukocytes counts $< 3.0 \times 10^9$/l, haemoglobin measurements < 9.0 g/dL, absolute number of neutrophils $< 1.0 \times 10^9$/l); or were pregnant. Patients who had previously received live attenuated vaccines other than the herpes zoster vaccine (within 6 months before study initiation, or planned within 6 months after discontinuation of study treatment) were also excluded.

Treatment

All patients were started on TOFA at a dose of 5 mg BID in combination DMRDs. In the absence of remission or low activity of the disease after 3 months, the dose of TOFA was escalated to 10 mg BID. Current treatment with DMARDs and glucocorticosteroids was continued. No change in the doses of these medications was allowed during the study period.

Measurements

Patient disease assessment

Demographic, disease and clinical characteristics were assessed at baseline and after 12 months of treatment. Disease duration, smoking, rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (ACCP), C-reactive protein, DAS28 [ESR], European League Against Rheumatism (EULAR) response, erosion on radiographs, current and past use of glucocorticoids, and biologic and non-biologic DMARDs were recorded. A patient was judged as a responder ("moderate" or "good") by the EULAR response criteria for RA [41] provided the DAS28 had reached a certain level of change from the study start in relation to the value attained. A decrease in DAS28 by more than 1.2 in combination with an end point DAS28 of 3.2 or less defined a good responder. A moderate responder must either have decreased by more than 1.2 while having attained any DAS28 over 3.2, or have decreased by less than 1.2 but by more than 0.6 in combination with an end point DAS28 not exceeding 5.1.

Cardiometabolic profile

Weight, height, waist circumferences, blood pressure and information on cholesterol-lowering, antihypertensive, antidiabetic drugs were obtained from all patients at baseline and after 12 months of treatment. BMI was calculated as body weight (kg) divided by height (m^2). BMI categories were defined as underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–< 25 kg/m^2), overweight (BMI 25–< 30 kg/m^2), obese (BMI 30–< 35 kg/m^2) and severely obese (BMI 35–< 40 kg/m^2) by World Health Organization definitions. 'Stable' weight was defined as a change of less than ± 2% of baseline weight per year. Abdominal obesity (AO) was diagnosed if waist circumference was > 94 cm in men and > 80 cm in women. AH was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or in case of antihypertensive therapy. Metabolic syndrome was defined according the International Diabetes Federation (IDF) criteria [42]. Fasting glucose and lipid profile [total cholesterol (TC), LDL-C, HDL-C, and TG] were measured. The atherogenic index (TC/ HDL-C) was then calculated. All patients underwent duplex scanning of the carotid arteries prior to the start of therapy and after 12 months of treatment with TOFA.

Statistical analysis

Statistical analyses were performed by SPSS 15.0 software. Distribution of all parameters was checked by the Kolmogorov–Smirnov test. The analyzed parameters were presented as median (interquartile percentiles). The difference of continuous variables in the various groups was determined by non-parametric Mann–Whitney or Kruskal–Wallis tests, when appropriate. To determine the reliability of changes in variables over time (linked samples), Wilcoxon test was used. The comparison of frequencies of discrete parameters was done by Chi-squared test. The relationships between continuous variables were analyzed by Spearman's rank correlation coefficients. Stepwise logistic regression was applied to isolate risk factors for BMI > 5%. Twosided p values < 0.05 were set as significant. VAI score was calculated as described [25] using the following sex-specific equations, with TG and HDL-C expressed in mmol/l.

$$\text{Males: VAI} = (\text{WC}/39.68 + (1.88 \times \text{BMI})) \times (\text{TG}/1.03) \times (1.31/\text{HDL-C}).$$

$$\text{Females: VAI} = (\text{WC}/36.58 + (1.89 \times \text{BMI})) \times (\text{TG}/0.81) \times (1.52/\text{HDL-C}).$$

Table 1 Clinical and laboratory characteristics of patients with RA at baseline and after 12 months of follow-up

Parameter	Baseline ($n=31$)	12 months ($n=31$)	p
Age (years)[a]	54 (40–62)		
Gender, m/f, n (%)	8/23 (26/74)		
Disease duration (months)[a]	39.5 (16.5–60.0)		
RF/ACCP—positivity, n (%)	77/74		
DAS28 [ESR][a]	5.1 (4.6–6.1)	3.1 (2.4–3.98)	< 0.001
Activity, n (%)			
Remission	0 (0)	9 (33)	
Low	0 (0)	6 (22)	
Moderate	12 (39)	11 (41)	
High	19 (61)	1 (4)	
C-reactive protein (mg/l)	18.7 (9.3–44.4)	1.7 (0.6–4.3)	< 0.001
Methotrexate, n (%)	30 (97)		
Methotrexate dose (mg/week)[a]	20 (20–25)		
Leflunomide, n (%)	1 (3)		
Leflunomide dose (mg/week)[a]	20		
Glucocorticoids, n (%)	9 (31%)		
Methylprednisolone dose, mg/day[a]	4 (4–6)		
bDMARDs in history, n (%)	10 (32)		
EULAR response, n (%)			
No effect		4 (15)	
Moderate effect		9 (33)	
Good effect		14 (52)	

[a]Data are expressed as median (25–75 percentiles)

ACCP anti-cyclic citrullinated peptide antibodies, *bDMARDs* biologic disease modifying antirheumatic drugs, *RF* rheumatoid factor

Optimal VAI cutoff points were: 2.52 (age < 30 years), 2.23 (age ≥ 30 and < 42 years), 1.92 (age ≥ 42 and < 52 years), 1.93 (age ≥ 52 and < 66 years) and 2.00 (age ≥ 66 years).

Results

Baseline patient characteristics

The study included 31 RA patients (women—74%, median age—54 years) (Table 1). Initially, all patients were prescribed TOFA at a dose of 5 mg BID in combination with methotrexate in 30 patients and with leflunomide in 1 patient. In eight (29%) patients, the dose of TOFA was escalated to 10 mg BID. Low doses of glucocorticoids (< 10 mg/day in terms of prednisone) were given to nine patients. Ten patients had previously received at least one bDMARD.

After 12 months, there was a significant decrease in disease activity according to DAS28 [ESR], CRP level; 55% of patients achieved remission or low RA activity, while 52% showed a good effect of therapy according to EULAR criteria (Table 1).

Most patients had TRFs of CVD prior to the start of therapy, 35.5% had elevated VAI values and 29% patients had metabolic syndrome (Table 2). Atherosclerotic plaques in the carotid arteries were detected in 61% of patients. No patients with coronary artery disease, MI and stroke in 'their history were enrolled in the study. Within 12 months of follow-up, 18 (58%) patients with early RA regularly took: statins—20 (65%), ACE inhibitors/sartans—16 (52%), beta-blockers—14 (45%), calcium antagonists—6 (19%), antiplatelet agents—3 (10%), diuretics—1 (3%) and antidiabetic drugs—2 (6%).

Dynamics of weight and body mass index during therapy with tofacitinib

In patients with RA, the median weight gain was 3 kg (4.2%) after 1 year of treatment with TOFA. Weight loss was observed in 3 (10%) patients, the lack of its dynamics in 5 (16%) and weight gain in 23 (74%) (Fig. 1). Among patients who gained weight ($n=23$), the median of its

Table 2 Dynamics of cardiometabolic indices at baseline and after 12 months of follow-up

Parameter	Baseline ($n=31$)	12 months ($n=31$)	p
Arterial hypertension, *n* (%)	19 (62)	19 (62)	ns
Systolic blood pressure (mmHg)[a]	120 (110–140)	120 (110–126)	ns
Diastolic blood pressure (mmHg)[a]	70 (60–80)	70 (63–80)	ns
Weight (kg)[a]	70 (63–81)	73 (65–86)	< 0.001
BMI (kg/m^2)[a]	26.4 (22.9–29.0)	26.8 (23.8–30.5)	< 0.001
BMI grades, *n* (%)			ns
Underweight	2 (6.5)	0 (0)	
Normal BMI	11 (35.5)	9 (29)	
Overweight	13 (41.9)	15 (48.4)	
Obesity grade 1	4 (12.9)	6 (19.4)	
Obesity grade 2	1 (3.2)	1 (3.2)	
WC (cm)[a]	87 (76–97)	92 (79–105)	< 0.001
HC (cm)[a]	102 (97–107)	105 (101–109)	< 0.001
WC/HC index[a]	0.82 (0.77–0.98)	0.86 (0.79–0.95)	ns
WC/HC index ≤ 0,9 (men), ≤ 0.85 (women), *n* (%)	14 (45)	16 (52)	ns
Abdominal obesity, *n* (%)	19 (61)	21 (69)	ns
Metabolic syndrome, *n* (%)	9 (29%)	9 (29%)	ns
Total cholesterol mmol/l[a]	5.09 (4.25–6.40)	5.34 (4.67–6.17)	0.08
Total cholesterol ≥ 5.0 mmol/l, *n* (%)	16 (52)	19 (62)	ns
LDL cholesterol (mmol/l)[a]	3.21 (2.75–4.33)	2.77 (2.55–3.70)	ns
LDL cholesterol ≥ 3.0 mmol/l, *n* (%)	20 (65)	13 (42)	0.06
HDL cholesterol (mmol/l)[a]	1.35 (1.06–1.86)	1.93 (1.34–2.13)	0.049
HDL cholesterol < 1.03 mmol/l for men, < 1.29 mmol/l for women, *n* (%)	13 (42)	5 (16)	0.005
TG (mmol/l)[a]	1.19 (0.76–1.60)	1.10 (0.76–1.60)	ns
TG ≥ 1.7 mmol/l, *n* (%)	5 (16)	6 (19)	ns
TC/ HDL cholesterol[a]	3.47 (2.71–4.89)	3.15 (2.43–3.85)	0.68
Glucose ≥ 5.6 mmol/l, *n* (%)	9 (29)	9 (29)	ns
Glucose (mmol/l)[a]	5.33 (4.85–5.76)	5.39 (5.17–5.79)	ns
Smoking, *n* (%)	8 (25)	6 (21)	ns
Postmenopausal, %	13 (57)	13 (57)	ns
Type 2 diabetes mellitus, *n* (%)	2 (6)	2 (6)	ns
VAI[a]	1.4 (0.9–2.6)	1.1 (0.7–1.9)	0.030
VAI above optimal cut-off points, *n* (%)	11 (35.5)	6 (19.0)	0.025

[a]Data are expressed as median (25–75 percentiles)

BMI body mass index, *HC* hip circumference, *HDL-C* high-density lipoproteins cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides, *VAI* visceral adiposity index, *WC* waist circumference

increase was 5% and 6 (26%) out of these had a weight gain of more than 10%.

BMI within the previous grading was preserved in 20 (65%) patients, one (3%) moved from the category of overweight to normal and ten (32%) to a higher category of BMI (Table 3). If before the start of treatment with TOFA, obesity was recorded in 16% of patients, then after 1 year of therapy in 23%.

The dynamics of BMI directly correlated with the initial DAS 28 [ESR] ($r=0.5$, $p=0.007$) and inversely with the baseline BMI ($r=-0.4$, $p<0.05$). Thus, patients with baseline DAS28 [ESR] < 4.9, 4.9 < 6, 6.0 + had an increase in BMI by 3%, 5% and 12%, respectively (Fig. 2).

Patients with baseline BMI < 25 kg/m^2, 25 < 30 kg/m^2, 30+ kg/m^2 had an increase in BMI by 8%, 4% and 3%, respectively, after 12 months (Fig. 3).

These indicators were introduced into the model of stepwise logistic regression (coefficient of multiple determination $R^2=0.42$). The resulting logistic model allows us to estimate the risk of an increase in BMI > 5% by the following indicators: BMI (< 25 kg/m^2, 25 < 30 kg/m^2, > 30 kg/m^2) odds ratio (OR) 0.199; 95% confidence interval (CI)

Fig. 1 BMI dynamics (%) 1 year after TOFA therapy

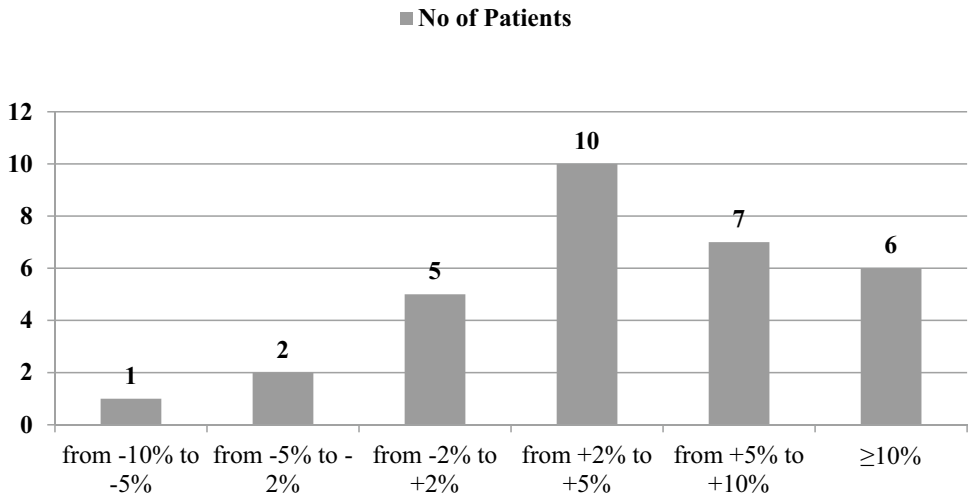

Table 3 The dynamics of the BMI category during treatment with TOFA

BMI category change	*n* (%)
Normal BMI–normal BMI	7 (23)
Overweight–overweight	9 (29)
Obesity grade 1–obesity grade 1	3 (10)
Obesity grade 2–obesity grade 2	1 (3)
Overweight–normal BMI	1 (3)
Underweight–normal BMI	2 (6)
Normal–overweight	4 (13)
Overweight–obesity grade 1	3 (10)
Obesity grade 1–obesity grade 2	1 (3)

BMI body mass index

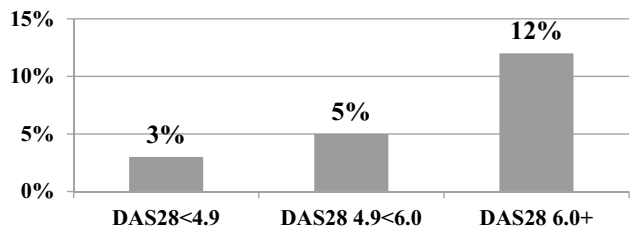

Fig. 2 The percentage of BMI changes during therapy with TOFA, depending on the baseline DAS28 [ESR]

0.049–0.812 ($p = 0.024$); DAS28 [ESR] (< 4.9, 4.9 < 6.0, 6.0 +) OR 5,141; 95% CI 1.345–19.654 ($p = 0.017$). There was no significant correlation between the baseline BMI and DAS28 [ESR].

The dynamics of BMI did not depend on gender, age, presence of TFRs of CVD, dose of TOFA, achieved RA activity, EULAR response, DAS 28 [ESR] dynamics, CRP level, use of antihypertensive, statins and antidiabetic drugs.

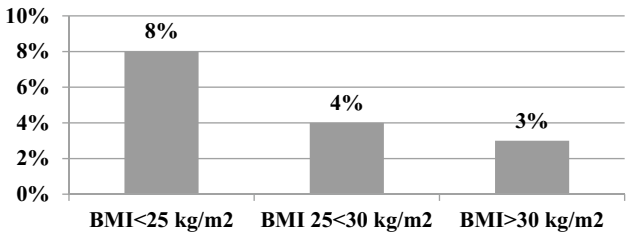

Fig. 3 The percentage of BMI changes during therapy with TOFA, depending on the baseline BMI

Dynamics of cardiometabolic indices during therapy with tofacitinib

During the follow-up, no serious cardiovascular events were recorded. The frequency of AH, smokers, type 2 diabetes mellitus and subclinical carotid atherosclerosis did not change (Table 2). An increase in the level of HDL cholesterol and a decrease in the frequency of its low values were noted. An increase in WC and HC was also detected, while the frequency of AO, elevated values of the WC/HC index and metabolic syndrome did not significantly change. The level of SBP, DBP, blood glucose, total cholesterol, LDL cholesterol, TG and atherogenic index did not significantly change. A decrease in VAI and frequency of its elevated values after 12 months were recorded (Table 2).

Discussion

In our single center, open label, prospective 1 year follow-up observational study, it was shown for the first time that 75% of the patients with moderate and high RA activity showed an increase in weight during treatment with TOFA (median

increase of + 3 kg, from 1 to 12 kg), and in 26% out of them by 10% or more. Thirty-two percent of RA patients moved to a higher category of BMI. Initially, higher RA activity and lower BMI were associated with a pronounced increase in BMI over time. At the same time, a decrease in VAI and frequency of its elevated values were recorded.

Our observations are consistent with data from other authors on weight gain during therapy with bDMARDs (iTNF-α and tocilizumab) in both RA and spondyloarthritis and psoriasis patients [29–32, 43–46]. At the same time, the number of patients who gained weight (50–75%), weight gain > 10% (25% of patients) and the severity of its increase (2–4 kg/year) are comparable. Weight gain during therapy with TOFA raises questions about the cardiovascular and metabolic neutrality of the drug. Obesity, especially abdominal, is associated with chronic low-grade inflammation and progression of metabolic and CV disorders [4]. TOFA, being a reversible inhibitor of JAKs, can lead to a decrease in JAK3 activity. JAK3 plays a key role in the pathogenesis of obesity and its associated metabolic syndrome [47]. JAK3 is needed in the intestines to maintain the mucosal barrier, reducing the infiltration of intestinal tissue by macrophages and neutrophils. Reduction in the level of JAK3 leads to weight gain, chronic inflammation of the intestinal mucosa, deterioration of glucose metabolism, hyperinsulinemia and fatty hepatosis. Also, blocking the JAK/Stat3/PI3K-dependent pathway can lead to leptin resistance, IR, stimulation of angiogenesis in adipocytes and obesity [48].

On the other hand, effective control of inflammation can be one of the treatments for rheumatoid cachexia. In patients with high RA disease activity, there was a decrease in muscle mass at comparable levels of fat mass compared with the control group, and one-third of the patients had muscle mass characteristic of sarcopenia [46]. Rapid weight loss is a more accurate predictor of overall mortality in RA than absolute weight and may explain the obesity paradox [17]. Thus, loss of body weight (more than 3 kg/m^2/year and more than 10% per year) is a predictor of CV mortality and mortality from cancer (OR 2.27, 2.31), regardless of the absolute BMI. On the contrary, overweight is associated with a cardioprotective effect (OR - 0.59), which may reflect the absence of significant weight loss against the background of high RA disease activity. With a prospective 40-year follow-up, it was shown that severe weight loss (more than 13 kg) after the diagnosis of RA was associated with an increase in mortality compared to maintaining a stable weight, whereas weight gain was not associated with a subsequent increase in mortality [18]. The treatment with iTNF-α is associated with a decrease in total and CV mortality, despite an increase in patient weight. Recent evidence suggests a decrease in rheumatoid cachexia and an improvement in metabolic parameters during therapy with iTNF-α and tocilizumab. Tournadre et al. [46] showed that after 1 year of treatment with tocilizumab, a significant increase in BMI due to muscle mass (appendicular and skeletal) was observed without changing the mass of adipose tissue. Redistribution of adipose tissue in a favorable type was noted, with a decrease in the body/peripheral fat ratio and an increase in subcutaneous fat. TOFA can also reduce sarcopenia, leading to a decrease in the levels of TNF-α and IL-6, which play a key role in enhancing the catabolism of muscle cells, even with adequate nutrition. This is indirectly confirmed by our results on a more significant increase in BMI over time (> 5%) in patients with initially higher activity and low BMI. Similar results were obtained by other authors: baseline BMI was inversely correlated with weight gain over the course of therapy with iTNF-α in patients with RA [31]. In patients with spondyloarthritis, high baseline activity was weight gain risk factor [29]. Perhaps, the loss of muscle mass is more pronounced in patients with high activity and body mass deficiency, and TOFA contributes to its recovery. However, according to the multivariate analysis, the initial indicators of activity and BMI influenced the growth of BMI in dynamics independently of each other. TOFA, like iTNF-α, can also have indirect positive effects on muscle mass through improved overall patient health. Patients with high RA activity report loss of appetite, increased fatigue and decreased physical activity, which improves with a decrease in the activity of the disease. In all studies, the effect of iTNF-α and tocilizumab on weight was small (2–4 kg/year). However, in some patients, weight gain on the background of tocilizumab led to the cancellation of therapy [33].

In our study, we assessed the dynamics of VAI during the treatment with TOFA. VAI is directly related to cardiometabolic risk (hypertension, impaired carbohydrate metabolism, cardiovascular events). Despite the increase in BMI there was a significant decrease in VAI and the frequency of its elevated values during therapy with TOFA, which can have a positive effect on CVR. Moisan et al. [49] revealed a specific effect of TOFA on adipose tissue. The authors showed the appearance of a new generation of brown adipose tissue ("brown-like" adipocytes) in the depot of white adipose tissue and a decrease in the total mass of fat under the influence of TOFA. White adipose tissue retains excess energy and performs a large number of endocrine functions. Brown adipose tissue helps to maintain body temperature, it is involved in lipid oxidation, reduces IR and protects against obesity and diabetes. Activation of brown adipose tissue also regulates the transport of lipoproteins rich in triglycerides and prevents their accumulation in the blood. Using PET/CT, it has been found that adults have brown adipose tissue with thermogenic activity [48]. Its presence is inversely correlated with obesity, BMI, hyperglycemia, therefore agents with white-to-brown potential are of increased interest. TOFA can become a drug that improves not only the course

of RA, but also comorbid states—metabolic syndrome, type 2 diabetes mellitus and CVR.

The limitations of this study are mainly related to the small sample size. However, despite the low number of patients, we were able to observe a significant change in BMI and VAI with TOFA treatment. The absence of a control group does not allow us to speak about the specific effect of TOFA on weight and cardiometabolic profile in patients with RA. Most patients had TRFs of CVD and atherosclerotic plaques prior to the start of therapy. The presence of CVD was not an inclusion or exclusion criteria in the study. RA patients are characterized by a high frequency of arterial hypertension, dyslipidemia, and subclinical atherosclerosis. Our results are consistent with literature data. Sixty-five percent of patients received statins (as in the study by Tournadre [46]), which could have a positive effect on the lipid profile and VAI. In our study, no methods were used to differentiate muscle and adipose tissue. Further studies are needed to determine how weight gain on the background of TOFA occurs (muscle or adipose tissue, how fat distribution changes) and what effects this may have on overall health and CV outcomes, as far as they are comparable to the effects of DMARDs.

Acknowledgements We would like to thank Elena L. Luchikhina and Dmitry E. Karateev for contributing to data collection and sharing additional data on the study.

Author contributions DSN and EVU contributed to the conception and design of the study, data collection and analysis, manuscript writing and final approval of the manuscript. IGK, ASM, NVD and EIM contributed to data collection and analysis, critical revision and final approval of the manuscript. TVP made substantial contributions to the conception and design, revision of draft manuscript and approval of the final version to be published. All authors read and approved the final version of the manuscript.

Funding There was no targeted funding relevant to this article Pfizer was not involved in the conduct of the study, the data analysis, manuscript preparation, the writing of the manuscript or the decision to submit the manuscript.

Conflict of interest There are no potential conflicts of interest relevant to this article.

Study participants The research involved human participants.

Ethical approval All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol had been approved by the local ethics committee in V.A. Nasonova Research Institute of Rheumatology (protocol #4, 11th of December 2014).

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Agca R, Heslinga SC, Rollefstad S et al (2017) EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 76:17–28
2. Crowson CS, Matteson EL, Davis III JM, Gabriel SE (2013) Contribution of obesity to the rise in incidence of rheumatoid arthritis. Obesity fuels the upsurge in rheumatoid arthritis. Arthr Care Res 65(1):71–77
3. Qin B, Yang M, Fu H et al (2015) Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. Arthritis Res Ther 17:86
4. Galic S, Oakhill JS, Steinberg GR (2010) Adipose tissue as an endocrine organ. Mol Cell Endocrinol 316(2):129–139
5. Symmons DP, Bankhead CR, Harrison BJ et al (1997) Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care-based incident case-control study in Norfolk, England. Arthr Rheum 40:1955–1961
6. Dar L, Tiosano S, Watad A et al (2017) Are obesity and rheumatoid arthritis interrelated? Int J Clin Pract. https://doi.org/10.1111/ijcp.13045
7. Albrecht K, Richter A, Callhoff J et al (2016) Body mass index distribution in rheumatoid arthritis: a collaborative analysis from three large German rheumatoid arthritis databases. Arthritis Res Ther 18:149
8. Ajeganova S, Andersson ML, Hafstrom I (2013) Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: A long-term followup from disease onset. Arthr Care Res 65(1):78–87
9. Humphreys JH, Verstappen SM, Mirjafari H et al (2013) Association of morbid obesity with disability in early inflammatory polyarthritis: Results from the Norfolk Arthritis Register. Arthr Care Res 65(1):122–126
10. Vidal C, Barnetche T, Morel J, Combe B, Daien C (2015) Association of body mass index categories with disease activity and radiographic joint damage in rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol 42(12):2261–2269
11. George MD, Østergaard M, Conaghan PG, Emery P, Baker DG, Baker JF (2016) Obesity and rates of clinical remission and low MRI inflammation in rheumatoid arthritis. Ann Rheum Dis 76(10):1743–1746
12. van der Helm-van Mil AH, van der Kooij SM, Allaart CF et al (2008) A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis. Ann Rheum Dis 67(6):769–774
13. Joo YB, Bang SY, Ryu JA et al (2017) Predictors of severe radiographic progression in patients with early rheumatoid arthritis: Prospective observational cohort study. Int J Rheum Dis 20(10):1437–1446
14. Escalante A, Haas RW, del Rincon I (2005) Paradoxical effect of body mass index on survival in rheumatoid arthritis: role of comorbidity and systemic inflammation. Arch Intern Med 165(14):1624–1629
15. Wolfe F, Michaud K (2012) Effect of body mass index on mortality and clinical status in rheumatoid arthritis. Arthritis Care Res (Hoboken) 64(10):1471–1479
16. Mikuls TR, Fay BT, Michaud K et al (2011) Associations of disease activity and treatments with mortality in men with rheumatoid arthritis: results from the VARA registry. Rheumatology (Oxford) 50(1):101–109
17. Baker JF, Billig E, Michaud K et al (2015) Weight loss, the obesity paradox, and the risk of death in rheumatoid arthritis. Arthritis Rheumatol 67(7):1711–1717

18. Sparks JA, Chang SC, Nguyen US et al (2018) Weight change in the early rheumatoid arthritis period and risk for subsequent mortality among women with RA and matched comparators. Arthritis Rheumatol 70(1):18–29
19. George MD, Baker JF (2016) The obesity epidemic and consequences for rheumatoid arthritis Care. Curr Rheumatol Rep 18(1):6
20. England BR, Baker JF, Sayles H et al (2018) Body mass index, weight loss, and cause-specific mortality in rheumatoid arthritis. Arthritis Care Res (Hoboken) 70(1):11–18
21. Frasca D, Blomberg BB, Paganelli R (2017) Aging, obesity, and inflammatory age-related diseases. Front Immunol 8:1745
22. Vlietstra L, Meredith-Jones K, Stebbings S et al (2017) Waters sarcopenic obesity is more prevalent in osteoarthritis than rheumatoid arthritis: are different processes involved? Rheumatology 56:18161818
23. Melmer A, Lamina C, Tschoner A et al (2013) Body adiposity index and other indexes of body composition in the SAPHIR study: association with cardiovascular risk factors. Obesity (Silver Spring) 21(4):775–781
24. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, Galluzzo A, AlkaMeSy Study Group (2010) Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care 33:920–922
25. Amato MC, Giordano C, Pitrone M, Galluzzo A (2011) Cut-off points of the visceral adiposity index (VAI) identifying a visceral adipose dysfunction associated with cardiometabolic risk in a Caucasian Sicilian population. Lipids Health Dis 10:183
26. Zhang Y, Lu N, Peloquin C, Dubreuil M et al (2017) Improved survival in rheumatoid arthritis: a general population-based cohort study. Ann Rheum Dis 76(2):408–413
27. Kerola AM, Nieminen TV, Virta LJ et al (2015) No increased cardiovascular mortality among early rheumatoid arthritis patients: a nationwide register study in 2000–2008. Clin Exp Rheumatol 33(3):391–398
28. Holmqvist M, Ljung L, Askling J et al (2018) Mortality following new-onset rheumatoid arthritis: has modern rheumatology had an impact? Ann Rheum Dis 77(1):85–91
29. Mahe E, Reguia Z, Barthelemy H et al (2014) Evaluation of risk factors for body weight increment in psoriatic patients on infliximab: a multicentre, cross-sectional study. JEADV 28:151–159
30. Alcorn N, Tierney A, Wu O, Gilmour H, Madhok R (2010) Impact of anti-tumour necrosis factor therapy on the weight of patients with rheumatoid arthritis. Ann Rheum Dis 69:1571
31. Brown RA, Spina D, Butt S, Summers GD (2012) Long-term effects of anti-tumour necrosis factor therapy on weight in patients with rheumatoid arthritis. Clin Rheumatol 31:455–461
32. Gisondi P, Cotena C, Tessari G, Girolomoni G (2008) Anti–tumour necrosis factor- α therapy increases body weight in patients with chronic plaque psoriasis: a retrospective cohort study. JEADV 22:341–344
33. Younis S, Rosner I, Rimar D (2013) Interleukin 6 blockade-associated weight gain with abdominal enlargement in a patient with rheumatoid arthritis. J Clin Rheumatol 19(1):48–49
34. Lee YH, Bae SC, Song GG (2015) Comparative efficacy and safety of tofacitinib, with or without methotrexate, in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. Rheumatol Int 35(12):1965–1974
35. Charles-Schoeman C, Burmester G, Nash P et al (2016) Efficacy and safety of tofacitinib following inadequate response to conventional synthetic or biological disease-modifying antirheumatic drugs. Ann Rheum Dis 75(7):1293–1301
36. Cohen SB, Tanaka Y, Mariette X et al (2017) Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis 76(7):1253–1262
37. Charles-Schoeman C, Fleischmann R, Davignon J et al (2015) Potential mechanisms leading to the abnormal lipid profile in patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. Arthritis Rheumatol 67(3):616–625
38. Pérez-Baos S, Barrasa JI, Gratal P et al (2017) Tofacitinib restores the inhibition of reverse cholesterol transport induced by inflammation: understanding the lipid paradox associated with rheumatoid arthritis. Br J Pharmacol 174(18):3018–3031
39. Kume K, Amano K, Yamada S et al (2017) Tofacitinib improves atherosclerosis despite up-regulating serum cholesterol in patients with active rheumatoid arthritis: a cohort study. Rheumatol Int 37(12):2079–2085
40. Aletaha D, Neogi T, Silman A et al (2010) The 2010 American College of Rheumatology/European League against rheumatism classification criteria for rheumatoid arthritis. Ann Rheum Dis 69:1580–1588
41. Van Gestel AM, Haagsma CJ, Van Riel PLCM (1998) Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 41:1845–1850
42. Alberti KG, Eckel RH, Grundy SM et al (2009) Harmonizing the Metabolic Syndrome A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120(16):1640–1645
43. Younis S, Rosner I, Rimar D et al (2013) Weight change during pharmacological blockade of interleukin-6 or tumor necrosis factor-α in patients with inflammatory rheumatic disorders: a 16-week comparative study. Cytokine 61:353–355
44. Engvall I-L, Tengstrand B, Brismar K, Hafström I (2010) Infliximab therapy increases body fat mass in early rheumatoid arthritis independently of changes in disease activity and levels of leptin and adiponectin: a randomised study over 21 months. Arthritis Res Ther 12:R197
45. Briot K, Garnero P, Le Henanff A et al (2005) Body weight, body composition, and bone turnover changes in patients with spondyloarthropathy receiving anti-tumour necrosis factor a treatment. Ann Rheum Dis 64:1137–1140
46. Tournadre A, Pereira B, Dutheil F et al (2017) Changes in body composition and metabolic profile during interleukin 6 inhibition in rheumatoid arthritis. J Cachexia Sarcopenia Muscle 8(4):639–646
47. Mishra J, Verma R, Alpini G, Meng F, Kumar N (2015) Role of Janus Kinase 3 in Predisposition to Obesity-associated Metabolic Syndrome. J Biol Chem 290(49):29301–29312
48. Al-Suhaimi EA, Shehzad A (2013) Leptin, resistin and visfatin: the missing link between endocrine metabolic disorders and immunity. Eur J Med Res 18:12
49. Moisan A, Lee YK, Zhang JD et al (2015) White-to-brown metabolic conversion of human adipocytes by JAK inhibition. Nat Cell Biol 17(1):57–67