Body mass index and response to infliximab in rheumatoid arthritis

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Abstract

Objective

Excess adipose tissue in obese individuals may have immunomodulating properties and pharmacokinetics consequences. Previous studies have suggested that obesity could negatively affect the response to anti-TNF-α agents, notably infliximab (IFX). We aimed to determine whether body mass index (BMI) is involved in the response to IFX in rheumatoid arthritis (RA).

Methods

We retrospectively examined data for 76 RA patients receiving IFX. BMI was calculated before treatment, and change from baseline in DAS28, pain on a visual analog scale, erythrocyte sedimentation rate, C-reactive protein level, tender and swollen joint count was analysed at 6 months after treatment. The primary outcome was decrease in DAS28 ≥1.2. Secondary outcomes were good response and remission according to EULAR.

Results

At baseline, the median [interquartile range] BMI was 26.6 [22.6–30.6] kg/m^2. The number of patients with normal weight, overweight and obesity was 25, 29 and 22. In multivariable analyses, IFX treated patients with lower BMI showed a more frequent DAS28 decrease ≥1.2 (25.5 [22.3–28.3] vs. 28.0 [23.2–32.5], p=0.02, odds ratio [OR] 0.88 [95% confidence interval 0.79–0.98]), EULAR good response (25.3 [21.9–27.5] vs. 27.5 [24.3–31.2], p=0.03, OR 0.87 [0.76–0.99]) and EULAR remission, although not significant (25.3 [21.9–26.4] vs. 27.5 [23.2–30.9], p=0.14, OR 0.88 [0.75–1.04]).

Conclusion

Obesity may negatively influence the response to IFX in RA. These data could help physicians to choose biologic agents for obese RA patients.

Key words
obesity, infliximab, rheumatoid arthritis

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Introduction

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health (1). A crude population measure of obesity is body mass index (BMI). Individuals with a BMI of ≥30 kg/m^2 are considered obese. Pharmacokinetic variables such as drug clearance and volume of distribution may be influenced by overweight and obesity (2). In addition, adipose tissue can exert both endocrine and immune effects on multiple other organs through the release of adipocytokines (3), which may contribute to the pathogenesis of several inflammatory conditions including rheumatoid arthritis (RA) (4). To date, the role of fat tissue in RA is unclear (5). Previous studies of RA found obesity prevalent in 18% to 31% of patients (6, 7). Overweight was noted in more than 60% of patients (6, 7). Obesity is associated in some studies with increased risk of RA (8, 9) and might have a protective effect early during the disease (10-12). In addition, weight loss and subsequent reduced BMI are linked to high RA activity (13). These results suggest a possible association of fat tissue and RA-related inflammation.

Recent reports showed a negative association of BMI and response to infliximab (IFX) in both RA (14, 15) and ankylosing spondylitis (AS) (16), which suggests that fat mass may affect the response to biologic agents. To date, pathophysiological mechanisms of how BMI influences IFX response remain unclear. One hypothesis could be the pharmacokinetic consequences of a high BMI on the response to intravenous drugs. BMI might be a predictive factor of IFX response in RA. In terms of the critical issue of identifying predictors of response to biologics, we aimed to investigate whether the BMI could affect the IFX response in RA.

Patients and methods

Study population

We performed a single-centre retrospective study of 76 RA patients who received IFX. All individuals fulfilled the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA (17) and had active RA according to the EULAR recommendations (18). Patients were identified by treating rheumatologists and by searching available electronic medical and pharmacy records with the keyword infliximab. Data were collected by SO and AG on computer records or by hospital charts. All patients receiving IFX since January 2005 to January 2012 were analysed. Data were collected in the Rheumatology department, biotherapy unit of the Bichat Hospital, Paris France. A nurse systematically assessed both weight and height at each visit. The erosive status was determined by presence of the term "erosive" in hospital x-ray charts of hands and foot and/or clinically involved joints at baseline. A senior rheumatologists performed joint counts.

The following data were collected at baseline (M0) and at month 6 (M6): BMI; gender; age; disease duration; disease activity score in 28 joints (DAS28); pain on a visual analogue scale (VAS, 0–100 mm); tender joint count (TJC) and swollen joint count (SJC) in 28 sites; anti-CCP antibodies and rheumatoid factor (RF) status; erosive status; use of disease-modifying anti-rheumatic drugs (DMARDs), corticosteroids or previous biologic agents; erythrocyte sedimentation rate (ESR); and C-reactive protein (CRP) level. BMI was calculated as weight in kilograms divided by height in square meters. According to the World Health Organization (WHO) criteria, normal BMI was defined as <25 kg/m^2, overweight 25–30 kg/m^2, and obesity ≥30 kg/m^2 (1). Infliximab was given intravenously at 3 mg/kg with a loading regimen at weeks 0, 2 and 6 and thereafter every 8 weeks according to national recommendations (19).

Clinical response was assessed after 6 months of IFX therapy. The primary efficacy endpoint was decrease in DAS28 ≥1.2. Secondary response criteria were proportion of patients achieving EULAR good response and EULAR remission (20). A good response was defined as a decrease in DAS28 ≥1.2 and low disease activity ≤3.2. EULAR remission was defined as final DAS28 <2.6. Local institutional review board (n.12-081) approved the study, and written informed consent was obtained from all subjects in the study.

Statistical analysis

Continuous variables are expressed as mean (SD) or median (interquartile range [IQR]). Categorical variables are expressed as frequencies and percentages. Comparisons between categorical variables involved the Pearson chi-square test. Student's *t*-test (two-tailed) was used to compare normally distributed continuous variables and Wilcoxon rank-sum test to compare continuous variables not normally distributed. We used logistic regression to determine variables associated with each of the three efficacy endpoint of IFX at M6. The models analysing response to IFX included BMI as a continuous variable and the following variables of adjustment: gender, age, disease duration, RF and anti-CCP status, previous anti-TNF-α therapies, concomitant DMARDs therapies, erosive status, CRP and DAS28 at baseline. Statistical analysis involved use of SAS v. 9.2 (SAS Inst., Cary, NC). $p<0.05$ was considered statistically significant.

Results

Characteristics of RA patients at baseline

Baseline demographic and clinical features of included patients are in Table I. A total of 76 RA patients received 6 months IFX therapy. The mean number of IFX infusion was 22.4.

At M0, the median [IQR] BMI was 26.6 [22.6–30.6] kg/m^2. In accordance with the WHO definition (1), the distribution of patients with normal weight, overweight and obesity was 25 (32.9%), 29 (38.2%) and 22 (28.9%), respectively. The 3 BMI groups did not differ in RA covariates, notably DAS28, at baseline (Table I) but there were significantly less overweight patients previously treated with anti-TNF-α than among normal weight or obese patients.

BMI and response to IFX after 6 months of therapy

• *Primary response criteria: DAS28 decrease ≥1.2*

In all, 41 (53.9%) RA patients achieved the primary response criteria.

In univariate analysis, the median BMI was lower for patients with than without a response (25.5 [22.3–28.3] *vs*. 28.0 [23.2–32.5]) but not significantly ($p=0.12$). This difference was significant in multivariable analysis ($p=0.0251$, odds ratio [OR] 0.88 [95% confidence interval 0.79–0.98]) adjusted on gender, age, disease duration, RF and anti-CCP status, previous anti-TNFα therapies, concomitant DMARDs therapies, erosive status, CRP and DAS28 at baseline (Figure 1). CRP and DAS28 at baseline were also significantly associated with the response criterion of decrease in DAS28 ≥1.2, ($p=0.04$, OR 0.97 [0.94–0.99] and $p<0.0001$, OR 4.28 [2.06–8.89], respectively).

When patients were dichotomised according to the 3 WHO BMI categories, only obesity was associated with absence of response ($p=0.0367$, OR 0.17 [0.03–0.92]).

• *EULAR good response and remission*

After 6 months of IFX therapy, 18 (23.7%) and 10 (13.2%) RA patients achieved EULAR good response and remission, respectively.

The median BMI was lower for patients with than without EULAR good response (25.3 [21.9–27.5] *vs*. 27.5 [24.3–31.2]) and patients with than without remission (25.3 [21.9–26.4] *vs*. 27.5 [23.2–30.9]), but not significantly ($p=0.07$ and $p=0.12$, respectively).

In multivariable analysis adjusted on gender, age, disease duration, RF and anti-CCP status, previous anti-TNF-α therapies, concomitant DMARDs therapies, erosive status, CRP and DAS28 at baseline, the BMI was significantly lower for patients with than without EULAR good response ($p=0.0334$, OR 0.87 [0.76–0.99]), but not for patients with than without remission ($p=0.14$, OR: 0.88 [0.75–1.04]) (Fig. 1).

Male gender and absence of previous anti-TNF-α were also significantly associated with a better proportion of good EULAR response (OR 7.61 [1.02–56.95], $p=0.048$ and OR 15.62 [1.52–160.17], $p=0.02$, respectively).

Table I. Baseline characteristics of RA patients receiving infliximab by 3 BMI categories.

	Whole population n=76	BMI <25 kg/m^2 n=25	BMI 25–30 kg/m^2 n=29	BMI >30 kg/m^2 n=22	*p*-value
Age (years)	49.1 [42.3-55.8]	46.5 ± 10.9	48.0 ± 9.8	51.4 ± 10.7	NS
Female gender (n, %)	63 (83)	18 (72)	26 (90)	19 (86)	NS
Disease duration (years)	8.0 [2.0-12.5]	10.0 ± 11.9	9.4 ± 6.9	7.6 ± 6.4	NS
RF+, n (%)	60 (79)	19 (76)	26 (90)	15 (68)	NS
Anti-CCP+, n (%)	65 (86)	21 (84)	25 (86)	19 (86)	NS
Erosive status, n (%)	63 (83)	20 (80)	27 (93)	16 (73)	NS
DAS28	5.6 [4.3-6.4]	5.3 ± 1.6	5.5 ± 1.4	5.3 ± 1.1	NS
ESR (mm), median [IQR]	28 [16-40]	22 [9-44]	30 [16-44]	27 [17-36]	NS
Pain on a VAS (0-100 mm)	60.7 ± 24.1	57.5 ± 27.9	58.5 ± 25.0	67.7 ± 18.9	NS
CRP (mg/l), median [IQR]	14.0 [5.0-30.0]	12 [5-30]	19 [8-24]	14 [5-30]	NS
DMARDs, n (%)	66 (87)	21 (84)	28 (97)	17 (77)	NS
Previous anti-TNF-α, n (%)	20 (27)	8 (33)	3 (10)	9 (41)	0.03
Corticosteroids use, n (%)	71 (93)	24 (96)	27 (93)	20 (91)	NS
Corticosteroids dose (mg/day), median [IQR]	10.0 [7.0-14.0]	10.0 [7-15]	10.0 [6-12]	10.0 [7-12]	NS

Data are mean ± SD unless indicated.

BMI: body mass index; RF: rheumatoid factor; DAS28: disease activity score in 28 joints; ESR: erythrocyte sedimentation rate; IQR: interquartile range; DMARDs: disease-modifying anti-rheumatic drugs; CRP: C-reactive protein; VAS: visual analogue scale; NA: not applicable.

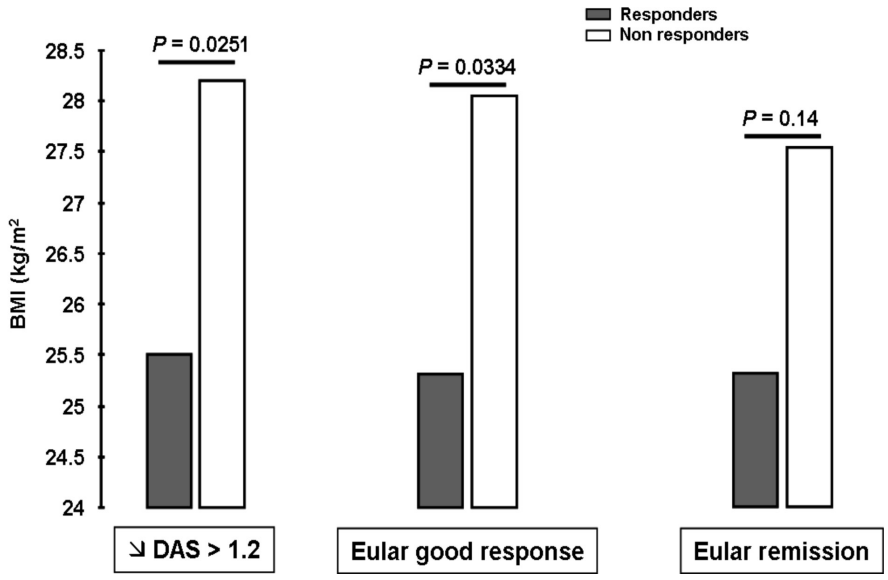

Fig. 1. BMI in RA patients treated with IFX according to the response criteria (multivariable analysis). Body mass index of patients with rheumatoid arthritis receiving infliximab by 3 criteria of response to therapy (multivariable analysis). BMI: body mass index; DAS: disease activity score; IFX: infliximab.

– Supplementary criteria

In multivariable analysis, low BMI was associated with decreased ΔDAS28 (p=0.0073), ΔSJC (p=0.0193) and corticosteroids use (p=0.0477). Corticosteroids use was decreased for 85%, 50% and 57% of normal, overweight and obese patients at M6, respectively. A tendency was found for ΔVAS (p=0.0872), ΔCRP (p=0.0951) but not ΔESR (p=0.3478) and ΔTJC (p=0.8574).

Discussion

Excess adipose tissue in obese individuals may have immunomodulating properties and pharmacokinetics consequences (2, 3). Obesity plays a role in several chronic disorders such as cardiovascular diseases and osteoarthritis (21) and its prevalence is increased in these diseases (22). Obesity might be a risk factor of RA developing from undifferentiated arthritis (23) and is associated with decreased radiographic evidence of disease progression in RA (11). Here, we investigated whether BMI could affect the response to IFX for RA at 6 months. Of note, our results demonstrated that increased BMI, notably obesity, was associated with lower response (decrease in DAS28 ≥1.2) to IFX and lower rate of Eular good response. Patients with increased BMI had also significant lower decrease of DAS28, SJC and use of steroids.

The negative impact of obesity on response to IFX is in agreement with previous findings (summarised in Table II). Klaasen *et al*. first suggested that, after 16 weeks of treatment with

Table II. Body mass index and response to anti-TNF-α therapies in inflammatory rheumatic disorders.

References	Rheumatic condition	Molecules	Number of patients	Prevalence of obesity (%)	Response criteria	Results
Klaasen *et al*. 2011	RA	IFX	89	17	↘ DAS28 >1.2	↗ BMI = ↘ response
Gremese *et al*. 2013	RA	IFX, ETN, ADA	IFX: 154 ETN: 227 ADA: 260	10.3	DAS<2.6	OR : 0.89 IFX +++
Heimans *et al*. 2013	RA	MTX MTX+SLZ MTX + IFX	508	15	DAS<2.4	↗ BMI = ↘ response
Present study	RA	IFX	76	28.9	↘ DAS28 >1.2	↗ BMI = ↘ response IFX : OR 0.88
Ottaviani *et al*. 2012	SpA	IFX	155	24	BASDAI 50	OR 0.87
Gremese *et al*. 2013	SpA	IFX, ETN, ADA	IFX: 104 ETN: 31 ADA: 35	13.5	BASDAI 50	↗ BMI = ↘ response Obesity : OR 3.6 IFX +++
Eder *et al*. 2014	PsoA	DMARDs: 60% Anti-TNF-α: 15%	557	35	MDA	↗ BMI = ↘ response Overweight : OR 0.66 Obesity : OR 0.53
Di Minno *et al*. 2013	PsoA	Anti-TNF-α: 100%	270 Obeses: 135	50	MDA	↗ BMI = ↘ response HR : 3.98 (non-MDA)

RA: rheumatoid arthritis; SpA: spondyloarthritis; PsoA: psoriatic arthritis; DAS: disease activity score; IFX: infliximab; ADA: adalimumab; ETN : etanercept; OR: odds ratio; MDA: minimal disease activity; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; HR: hazard ratio; BMI: body mass index; DMARDs: disease-modifying anti-rheumatic drugs.

IFX, RA patients with increased BMI showed reduced DAS28 decrease (14). Furthermore, Gremese *et al*. found that obesity was a risk factor for poor remission in patients with longstanding RA treated with anti-TNF-α agents (15). Negative impact of BMI on response to combination RA treatment was also found by Heimans *et al*. (24). Of note, similar results were found in patients with spondyloarthritis (16, 25) and psoriatic arthritis (26, 27) who received anti-TNF-α therapies. Interestingly, in all studies, the decrease of response was mainly observed for IFX treatment.

Several hypotheses could explain the role of excess adipose tissue in RA response to treatments. Adipokines secreted in adipose tissue could increase the level of pro-inflammatory cytokines, thus leading to an inflammatory basal state. However, in our study, baseline CRP levels among the 3 BMI subgroups were similar (Table I). Of note, the influence of anti-TNF-α agents on adipokine levels remains unclear (reviewed in (28)). In the general population, adiposity is the main determinant of systemic inflammation whereas in RA, both RA disease activity and obesity reportedly contribute to circulating CRP concentrations. A series of studies addressed the implication of adipokines in RA and adiposity in patients with severe disease undergoing anti-TNF-alpha therapy. In this regard, in long-standing RA patients with active disease on periodical treatment with infliximab, adiponectin concentrations were negatively correlated with the triglycerides/HDL cholesterol ratio, total cholesterol/HDL cholesterol ratio and plasma glucose levels (29). In this cohort CRP levels correlated with circulating adiponectin concentrations, independent of age and gender. However, the body mass index (BMI) did not correlate with adiponectin levels (29). In the same cohort, a significant association between the mean ESR and CRP from disease diagnosis and ESR, CRP and platelet count at the time of the study and resistin levels was found (30). As disclosed for adiponectin, no correlation between resistin and BMI was observed (30). Interestingly, a positive correlation between BMI of these RA patients and serum level of leptin was observed (31). In this series on long-standing RA patients on periodical treatment with infliximab, circulating leptin concentrations were unrelated to disease activity but constituted a manifestation of adiposity as observed in non-RA subjects (31). In contrast, in the same cohort, visfatin levels were not associated with inflammation, disease activity, adiposity or metabolic syndrome (32).

Although the dose of IFX is weight based, variations in inter-individual serum concentration have been established in both RA (33, 34) and AS (35). Several obesity-related factors could alter IFX pharmacokinetics. The volume of distribution of a non-lipophilic drug such as IFX could be decreased by excess adipose tissue (2), thus leading to the restrictive negative effect of BMI on the IFX response as compared with an anti-TNFα agent subcutaneously administered (*i.e*. etanercept and adalimumab) (15). As well, reduced tissue perfusion and cardiac function in obese individuals (36) could lead to decreased IFX distribution.

Our study has some limitations. First, the study was retrospective, which is the major limitation, with potential bias of recruitment and interpretation. The predictive effect of BMI on IFX response should be investigated in prospective cohort. Finally, the design of this study did not allow for investigating the pharmacokinetics consequences of high BMI.

We have provided data obtained from a real life setting that can be of help in clinical practice. However, registries and prospective studies are mandatory confirm our results.

Conclusions

Obesity seems to be negatively associated with poor response to IFX in RA. Prospective studies are required to fully establish whether BMI is a predictive factor of response to IFX in RA. In line with the concept of personalised medicine, BMI is an easy tool to assess for the rheumatologist.

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