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Original Article

Body mass index as a driver of selection of biologic therapy in rheumatoid arthritis. Results from the US-CLARA study

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ABSTRACT

Purpose: Body mass index (BMI) demonstrated to influence the clinical response to different drugs in rheumatoid arthritis (RA). The aim of this study was to investigate the role of BMI in the achievement of remission in active RA patients starting the treatment with abatacept.

Methods: Data regarding 130 RA patients enrolled in the UltraSound-CLinical ARthritis Activity (US-CLARA) study were retrospectively analyzed. Patients were assessed at baseline (when starting abatacept treatment) and at 3- and 6-months. An extensive clinimetric evaluation, including a new ultrasound (US)/clinical composite disease activity index, termed US-CLARA, was performed at every timepoints. Outcome of interest of the study was the impact of BMI on the achievement of the Disease Activity Score 28-joints erythrocyte sedimentation rate (DAS28-ESR) or the ACR/EULAR Boolean remission criteria at 6 month.

Results: At 6-month 26 out of 130 patients were defined as responders to abatacept. Comparing the baseline characteristics of responders to non-responders, US-CLARA showed a statistically significant difference between the two groups. The logistic regression analysis showed that the two indipendent variables, predictive of treatment response (keeping the DAS28-ESR and/or Boolean remission criteria as dependent variable), were the self-tender joint count assessment ($p = 0.0412$) and the ultrasound score ($p = 0.0211$). No other baseline variable, notably BMI, was associated to 6-month abatacept response.

Conclusions: BMI does not influence the abatacept response in RA patients with active disease. During abatacept treatment, the clinical response can be achieved despite a condition of overweight or obesity.

1. Introduction

During the last years, the availability of the biologic agents has led to a revolution in the treatment chronic inflammatory arthritis. Nowadays, a wide range of molecules, covering a broad variety of pharmacological actions, is licensed for the therapy of rheumatoid arthritis (RA). However, despite the abundance of effective drugs, in the real-life setting the achievement of remission still represents a challenge in a significant number of patients.

The presence of comorbidities raises a major issue for achievieng remission in RA patients, demonstrating to impact the response to treatment [1]. Among comorbidities, obesity showed to deeply influence the effectiveness of disease modifying anti-rheumatic drugs (DMARDs) [2], as well as of certain biological therapies, in particular of anti-tumor necrosis factor (TNF) agents [3]. It has been demonstrated that adipose tissue represents an important player in inflammatory conditions and autoimmunity, and it is assumed that obesity is a low grade and chronic inflammatory state. Therefore, obesity may be considered a risk factor for developing immune mediated diseases, including RA [4].

Most of the data regarding the biological therapies in obese/overweight patients are disposable for anti-TNF agents. In RA, body mass index (BMI) is a predictor of treatment effectiveness, and obesity undoubtely decreases the clinical response to anti-TNF agents in RA [5,6]. The mechanisms of the less favourable response to anti-TNF agents in obese or overweight subjects is not fully understood yet. It has been hypothesized that adipocytokines and cytokines directly produced by fat can induce the resistance to TNF blockade [7].

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Thus, during the last years a great attention has been focused on the effectiveness of biologic agents with different mechanisms of action, including inteleukin (IL)-6 blockade (tocilizumab) and T cell co-stimulation inhibition (abatacept), in RA obese patients. In a recent post-hoc analysis including a large number of partecipants, abatacept demonstrated that the baseline BMI stratification does not influence the clinical effectiveness (remission) of both its subcutaneous (SC) or intravenous (IV) formulations [8].

Since replication of the results is a cornerstone in research, we aimed to confirm the recent findings in a different RA cohort, coming from the UltraSound-CLinical ARthritis Activity (US-CLARA) study [9].

In particular, the aim of the present study is to assess if BMI represent a clinical variable influencing the achievement of remission after six months in a cohort of patients with active RA starting abatacept.

2. Methods

2.1. Study design and inclusion criteria

This study is a post-hoc analysis of a multicenter, prospective, longitudinal study, carried out from September 2014 to March 2016 in 11 italian rheumatologic centers headed by the "Gruppo Italiano di Studio sulla Early Arthritis" (GISEA). The main aim of the primary work was to validate a new compositite disease activity index for RA, called US-CLARA. The detailed description of the index is provided in the original paper [9], and a brief summary of the US-CLARA features is listed below.

The study cohort was represented by 130 RA patients, all of them starting treatment with abatacept. The study lasted for the first six months of therapy, and patients were assessed at three visits (baseline, 3-month, 6-month). The inclusion criteria were: age 18–75 years, RA diagnosed according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria [10], and the presence of an "active" disease refractory to conventional DMARDs or to anti-TNF agents. Active RA was defined by the presence of at least three of the following features: erythrocyte sedimentation rate (ESR) $\geq$ 28 mm/1sthour or C-reactive protein (CRP) > 19 mg/L, swollen joint cout on 28 joints (28-SJC) > 5, tender joint count on 28 joints (28-TJC) > 6, morning stiffness $\geq$ 30 min. In this study both SC and IV abatacept formulations were admitted: 68 partecipants (52.3%) were treated with the SC weekly injection of abatacept (125 mg), while 62 subjects (47.7%) received the IV formulation. The cohort sample size was calculated on the estimate of the proportion of patients achieving remission after six months of treatment form the results of the "abatacept clinical program" (from 10% to 35%) [11–13]. The estimated number of patients enrolled was 125 under the assumption that the percentage of remission would be the 25%. The study was carried out according to the Declaration of Helsinki principles, the local ethic review board approval was obtained in each center. All the subjects signed the written informed consent to be enrolled in the study.

2.2. Clinimetric assessment

Demographic variables (including age, sex, disease duration, schooling, BMI), actual treatment, the presence and the titre of IgM-rheumatoid factor (RF) and of anti-citrullinated protein antibodies (ACPA) were collected at baseline.

For each visit the clinical assessment included the 28-SJC and 28-TJC, 10-points numerical rating scale (NRS) of pain, general health status (GH), and patient and physician global assessment of RA activity (PaGA and PhGA), while the laboratory evaluation included CRP (mg/dl) and ESR (mm/1sth).

According to the above mentioned variables, at baseline and quarterly were calculated the Disease Activity Score 28-joints (DAS28)-ESR, the DAS28-CRP, the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI).

Moreover, patients filled in three PROs, respectively the Recent-Onset Arthritis Disability (ROAD) questionnaire to assess function, the Rheumatoid Arthritis Disease Activity Index (RADAI), and the Clinical Arthritis Activity (PRO-CLARA) to evaluate patient-reported disease activity.

Lastly, in each visit, patients underwent the ultrasound (US) assessment of wrists, second and third metacarpophalangeal (MCP) joints, and second and third proximal interphalangeal (PIP) joints to define the US score. For each joint, the presence of a grade $\geq$ 1 of both B-mode and power-Doppler US (PDUS) (Outcome Measures in Rheumatology definition) [14] was considered as the presence of US-confirmed. In each joint, US synovitis was weighted according to the Thompson's articular index [15], then normalized to a 0–10 scale. The US score, combined with ROAD and with the self-administered TJC of RADAI, was required to compute the US-CLARA. An extensive discussion of ROAD, RADAI, PRO-CLARA, and US-CLARA is beyond the purposes of the present work. For a detailed description of these tools the reader can refer to the validation papers [9,16–19].

2.3. Statistical analysis

Data were stored into a Microsoft Excel database and analyzed with SPSS 11.0, and MedCalc 7.1.02 for statistical software packages for Windows XP.

Data are presented as means with standard deviations (SDs) or medians with interquartiles ranges.

Patients were distinguished in "responders" and "non-responders" at six months. Responders category included patients satisfying the DAS28-ESR definition and/or the Boolean criteria for remission according to ACR/EULAR definition [20,21].

Differences between groups have been evaluated using the Mann-Whitney *U* test.

Subsequently, demographic (age), laboratory (RF, ACPA, ESR, and CRP), and clinimetric parameters (BMI, US-score, self-TJC, ROAD, PaGA, and PhGA), recorded at baseline, were entered as possible explanatory variables in the multivariate logistic regression model, with responders category (DAS28-ESR and/or Boolean remission) at six months considered as dependent variable.

Finally, responders to abatacept treatment were categorized according to BMI (normal weight BMI < 25 kg/m^2, overweight 25 $\leq$ BMI $\leq$ 30 kg/m^2, obese BMI > 30 kg/m^2). The abatacept response in the BMI subgroups was evaluated analyzing the differences of the areas under the curves (AUCs) for the disease activity indices.

3. Results

3.1. Demographic and baseline characteristics

The mean (SD) age of the 130 partecipants (83.8% female) was 58.85 (11.78) years, with a mean (SD) disease duration of 11.21 (8.76) years, and a mean (SD) BMI of 26.38 (4.49). A detailed BMI summary statistic description and percentiles distribution of the study cohort is provided in Table 1.

The majority of the patients was ACPA (66.9%) and RF (64.6%) positive.

The mean (SD) baseline SDAI was 31.53 (9.81), while the mean (SD) baseline US-CLARA was 5.32. Exploring the US-CLARA subcomponents at baseline, the mean (SD) ROAD was 5.19 (2.16), the mean (SD) self-TJC was 4.87 (2.20), and the mean (SD) US score was 6.06 (2.74). Regarding the route of administration, 68 patients (52.3%) the subcutaneous abatacept treatment (125 mg/week), while 62 patients (47.7%) were treated with abatacept by monthly intravenous infusion according to baseline weight. Forty-four patients were already exposed to a previous biologic treatment (respectively, 19 patients to etanercept, nine to adalimumab, four to infliximab, three to certolizumab

Table 1
Summary statistic and percentiles distribution of body mass index in the whole cohort at baseline (130 patients).

Lowest value	18.39
Highest value	44.89
Arithmetic mean	26.38
95% confidence intervals for the arithmetic mean	25.18–26.81
Median	25.45
95% confidence intervals for the median	24.22–25.67
Variance	22.06
Standard deviation	4.49
Relative standard deviation	0.18 (18.07%)
Standard error of the mean	0.4120
Coefficient of skewness	1.0013 ($p < 0.0001$)
Coefficient of kurtosis	1.2682 ($p = 0.0234$)
Shapiro-Wilk test for normal distribution	W = 0.9360, reject Normality ($p < 0.0001$)
Percentiles	Mean (95% confidence interval)
2.5	19.90
5	20.23 (19.27–20.67)
10	20.77 (20.24–21.21)
25	23.03 (21.63–23.52)
75	28.71 (27.34–30.72)
90	32.53 (31.19–34.37)
95	34.41 (32.95–37.43)
97.5	35.51

pegol, two to golimumab, five to tocilizumab, and two to rituximab).

3.2. Responders vs non-responders features

After six months of treatment with abatacept, 26 patients achieved the DAS28-ESR and/or the Boolean remission criteria (responders). Comparing the baseline characteristics of responders vs non responders, without considering the traditional disease activity indeces, the three components of US-CLARA showed a statistically significant difference between the groups (ROAD, $p = 0.022$; self-TJC, $p = 0.005$; US score, $p = 0.001$) (Table 2).

The logistic regression analysis confirmed that the two indipendent variables, predictive of treatment response (keeping the DAS28-ESR and/or Boolean criteria satisfaction as dipendent variable), were the self-TJC ($p = 0.0412$) and the US score ($p = 0.0211$) (Table 3). Interestingly, no other investigated variable, in particular BMI, was related to or predictive of abatacept response.

Table 3
Logistic regression analysis using the "responders" category (modified Residual Minimal Disease Activity and/or Boolean criteria) as dependent variable.

Variable	Coefficient	Standard error	p
US-score (0–10)	−0.103631	0.047453	0.0211
Self-TJC (0–10)	−0.183666	0.096377	0.0412
ACPA (title)	−0.001552	0.000744	0.1444
Age (years)	−0.034452	0.021811	0.1483
RF (title)	0.001564	0.003113	0.3334
PaGA (0–10)	0.065675	0,076324	0.4543
ESR (mm/1sth)	−0.024554	0.009070	0.0569
PhGA (0–10)	0.064569	0.133407	0.4577
BMI (kg/m^2)	0.019445	0.032442	0.5346
ROAD (0–10)	−0.037463	0.097253	0.7127
CRP (mg/dl)	−0.013458	0.016344	0.3453
Previous biologic exposure	−0.013467	0.015142	0.3125

Abbreviations: US = ultrasound; TJC = tender joint count; ACPA = anti-citrullinated protein antibodies; RF = rheumatoid factor; PaGA = patient global assessment of disease activity; ESR = erythrocyte sedimentation rate; PhGA = physician global assessment of disease activity; BMI = body mass index; ROAD = Recent-Onset Arthritis Disability questionnaire; CRP = C-reactive protein.

4. Discussion

This post-hoc analysis clearly demonstrates that BMI does not influence the abatacept response in RA patients with active disease.

Moving in a broad range of RA treatment options, to understand the predictors of pre-treatment outcomes raised a major issue in the rheumatologic community. During the last years, the concept of personalized therapy evolved in RA thanks to discovery of predictive biomarkers [22].

Of course, to prescribe the right drug to the right patient could avoid the failure of the drug itself, helping to save time (fundamental for the treat-to-target strategy), to reduce the costs, to ameliorate the risk-benefit assessment [23] and, last but not least, to preserve patient from the burden deriving from pain, articular damage, and function impairment.

During the last years, the discovery and the great development of biomarkers allowed to start to consider a tailored medicine. The definition of biomarker is broad, referring to the category of the medical signs: "objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly" [24].

Table 2
Baseline demographic, laboratory, and clinimetric differences in rheumatoid arthritis patients "responders" or "non responders" after six months of abatacept treatment.

	Patients (n, 130)								
	Non responders (n, 104)				Responders (n, 26)				
	Mean	SD	Median	25–75 P	Mean	SD	Median	25–75 P	p*
BMI (kg/m^2)	26.98	4.57	25.31	22.98–30.80	26.13	3.83	25.77	23.76–28.89	n.s.
Age (years)	59.09	11.37	61.00	53.00–68.00	58.15	11.87	57.00	49.50–66.50	n.s.
Disease duration (years)	11.79	8.94	9.00	3.75–15.50	12.11	9.03	10.00	6.50–20.00	n.s.
PhGA (0 − 10)	6.11	1.98	6.00	5.00–8.50	5.93	2.10	6.50	5.50–7.50	n.s.
PaGA (0–10)	7.15	1.99	8.00	6.00–9.00	6.80	2.13	7.50	5.50–8.00	n.s.
CRP (mg/dl)	15.95	22.22	8.70	4.80–18.00	13.24	18.81	8.00	3.50–17.50	n.s.
ESR (mm/1sth)	38.86	21.82	25.50	22.00–53.50	35.75	20.50	26.00	19.00–50.50	n.s.
ACPA (title)	226.32	444.47	93.00	19.00–390.00	197.08	223.04	64.00	9.50–350.00	n.s.
RF (title)	157.97	195.36	60.00	16.50–164.00	146.28	203.52	44.00	8.97–199.95	n.s.
ROAD (0–10)	5.66	2.49	5.93	3.54–7.68	4.13	1.90	4.08	2.21–5.93	0.021
Self-TJC (0–10)	5.61	2.481	5.351	3.50–7.22	4.01	1.74	3.71	2.55–5.25	0.005
US-score (0–10)	6.61	2.61	6.90	4.31–8.55	4.60	2.18	4.51	3.43–6.77	0.001

Abbreviations: BMI = body mass index; PhGA = physician global assessment of disease activity; PaGA = patient global assessment of disease activity; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ACPA = anti-citrullinated protein antibodies; RF = rheumatoid factor; ROAD = Recent-Onset Arthritis Disability questionnaire; TJC = tender joint count; US = ultrasound.

* *p* values are for the test of overall difference for response category tested using Mann–Whitney U test.

While different laboratory biomarkers are not yet widely available in daily clinical practice (just think to protein biomarkers, flow cytometry biomarkers, single nucleotide polymorphisms, or transcriptomes) [23], BMI, intended as a clinical biomarker very easy to be computed, showed to be a predictor of worse outcomes in RA patients [2], and an eccessive BMI, meaning overweight or obesity, is a comorbid condition quite frequent in RA patients: the obesity prevalence in early RA is 12.4% [25].

Obesity itself is a cardiovascular risk factor [26] and, in patients with RA, may negatively influence the response of the treatment with a biologic agent.

The majority of the data have been collected with anti-TNF agents. In 2011, Klaseen and colleagues showed that even if infliximab dosage was properly based on body weight, the response in RA patients with a high BMI was inadequate [7]. In 2013, data coming from a wide cohort (640 patients) deriving from an Italian register, revealed that, after one year of anti-TNF therapy, only the 15.2% of the obese patients achieved the DAS28 remission vs the 32% of the subjects with a BMI $< 30\,kg/m^2$ [6].

However, the relationship between obesity and anti-TNF response is an unsolved issue. Recently, from data deriving from two large trials involving golimumab, it has been confirmed that obesity was associated with a low likelikehood ratio of reaching remission. At the same time, in the same obese patients the magnetic resonance imaging showed low activity similar to that of non-obese subjects [27].

More encouraging are the findings on tocilizumab. Pers and colleagues retrospectively studied the response (EULAR response criteria) after six months of tocilizumab therapy in RA patients, and found that it was not influenced by BMI [28]. Similar data have been obtained in a retrospective French survey involving 115 patients [29].

Good, but low the total number of patients studied, seemed to be the effectiveness of rituximab in obese RA patients [30].

Overall, the more robust evidence regarding the clinical response to a biologic agent in obese or overweight patients has been reported with abatacept.

Our finding corroborates those of the available studies, deriving from very large registries, such as the pan-European registry collaborataion for abatacept. In this study, involving 2015 RA patients (18.9% obese), it has been revealed that obese or non-obese subjects attained the same clinical response and the same retention rate during IV administration of abatacept [31].

D'Agostino and colleagues, in a recent elegant study, demonstrated how both SC and IV abatacept administration are associated with a good clinical reponse, regardless of body weight. Eventhough pharmacokinetic differences were detectable in plasma concentration of the drug between the route of administration and among BMI categories, the pharmacological effect of abatacept was not invalidated [8].

From the sonographic perspective, we demonstrated that the US score is a variable predictive of abatacept response. These findings are consistent with those of the APPRAISE study, in which abatacept showed to determine a rapid improvement in US, expecially in PDUS: early improvement signs can be detected after 1-week [32].

An atypia that emerges from this study, worthy of mention, is the lack of association of response to abatacept and the ACPA presence. It can be assumed that this finding is due to the relatively low title of the ACPA in the studied population.

The major strengths of our study are the large sample size and the multicenter nature, covering a wide range of RA patients, rigorously recruited in different settings. Instead, the major limitations of the study can be considered the relative low number of patients overweight or obese involved and the a posteriori design.

5. Conclusion

Abatacept efficacy is not affected by body weight in RA patients. During abatacept treatment, the clinical remission can be achieved despite a condition of overweight or obesity. Moving towards a more and more personalized medicine, this issue should be of aid to maximise the risk-benefit assessment for the single patient.

Competing interests and financial disclosures

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Authors' contributions

FS, GL, and GF conceived and designed the study and the protocol. FS and MDC carried out data interpretation and analysis. FS, MDC, GL, and GF wrote the paper. FI and EG were involved in drafting the article or revising it critically for important intellectual content. All authors approved the final version to be submitted for publication.

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