Obesity decreases clinical efficacy and levels of adalimumab in patients with ankylosing spondylitis

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ABSTRACT

Objective. *Obesity can be a factor that affects response to anti-TNF drugs. However, studies on patients with ankylosing spondylitis (AS) are rare. We aimed to determine whether obesity affects serum levels of adalimumab (ADL), and immunogenicity and clinical efficacy of the drug in patients with AS.*

Methods. *A cross-sectional study on 57 patients with axial AS receiving ADL was conducted. They received DMARD per standard of care at their rheumatologist's discretion. Patients' body mass index (BMI) was obtained when ADL treatment began. Clinical response was evaluated using the Spanish versions of the BASDAI index and the ASDAS ESR index. Serum concentrations of free ADL (trough level) and anti-ADL antibodies were measured using Promonitor-ADL and Promonitor Anti-ADL ELISA kits (Progenika Grifols SA, Spain), just prior to the next subcutaneous injection of ADL.*

Results. *Patients with BMI >30 kg/m^2 (obese) as opposed to BMI <25 kg/m^2 (normal), presented lower blood ADL levels [5.0 (5.52) vs. 9.14 (4.3), p=0.032], increased ASDAS scores (2.58 [0.79] vs. 1.9 [0.83], p=0.03), and shorter ADL treatment time: 1.01 [0.84] vs. (1.85 [1.65]; p=0.08]), and increased BASDAI results (5.04 [2.5] vs. 3.5 [1.88]; p=0.06). Obese patients showed a lower probability of clinical response to ADL versus non-obese patients with regard to achieving BASDAI ≤4 (OR: 3.5, 95%CI: 0.84–17.19; p=0.05) or ASDAS ≤2.1 (OR: 4.64, 95%CI: 1.02–24.13; p=0.02).*

Conclusion. *Of the AS patients receiving treatment with ADL, those that are obese had significantly lower serum ADL levels and decreased clinical response without an increase in immunogenicity.*

Introduction

Obesity increases the risk of developing illnesses such diabetes, atherosclerosis, or non-alcoholic fatty liver disease. Recently, obesity has also been linked to chronic inflammatory and autoimmune processes (1).

The fatty tissues of obese people release soluble mediators or adipokines, the significance of which with regard to the pathogenesis of inflammatory diseases, such as rheumatoid arthritis (RA), has been reported (1-3). Adipokines can increase the level of proinflammatory cytokines such as adiponectin, leptin, resistin or visfatin. Adipose tissue also contains coagulation mediators and complement factors, and IL1 and TNF (1), can increase their expression, which is tied to inflammatory diseases.

Various studies suggest that obesity can affect the volume of distribution and pharmacokinetics of drugs, meaning that it could alter the response to anti-TNFs (4), and decrease their efficacy in RA patients (5, 6). Furthermore, the presence of metabolic syndrome has been associated with a lower likelihood of achieving clinical remission in patients receiving anti-TNFs (7, 8). However, few studies have evaluated the influence of body mass index (BMI) in patients with ankylosing spondylitis (AS).

Although anti-TNF drugs are effective in patients with AS, up to 40% stop responding over time. Various studies have demonstrated the association between anti-TNF drug levels and clinical efficacy in patients with RA (9) or AS (10, 11). In some patients, the loss of efficacy is related to the appearance of anti-drug antibodies (ADA), depending on the drug and various factors: genetics, underlying disease, pharmacokinetics of the drug itself, or the combination with DMARDs, especially methotrexate. For adalimumab (ADL), around 30% of patients with AS develop ADA in the first year of treatment (10). It is likely that the increased frequency of ADA in patients with AS treated with ADL is due to the fact they are less likely to be treated in combination with DMARDs (9).

The objective of this study is to determine whether obesity affects ADL serum levels, and immunogenicity and clinical efficacy of the drug in patients with AS.

Materials and methods

From January 2014 to September 2015, 57 patients with AS and treated with ADL at our rheumatology clinic were

included. All had axial involvement, associated or not with peripheral arthritis, psoriasis or inflammatory bowel disease (IBD), based on the ASAS group classification criteria (12), all over the age of 18 years, and on treatment with subcutaneous ADL 40 mg (Humira®, Abbvie Laboratories, Madrid, Spain) every 14 days for at least 3 months. During treatment, at the discretion of the rheumatologist, patients could receive DMARDs such as methotrexate, leflunomide, sulfasalazine or azathioprine in IBD. Patients underwent an initial evaluation (cross-sectional) and continued to be monitored as standard clinical practice.

The study was approved by the local Ethics Committee, and patients signed informed consent forms for inclusion.

Data collection

The BMI was obtained when treatment with ADL began, and patients were placed in one of the three following categories: normal <25 kg/m^2, overweight: 25–30 kg/m^2, obese: >30 kg/m^2.

Information regarding age, sex, BMI, date of diagnosis of AS, laboratory data including, HLA-B27, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), previous and current treatment for AS, DMARDs and anti-TNF drugs received and duration of ADL treatment were recorded.

Clinical response

Clinical response was evaluated using the Spanish version of the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) index (13) and the ASDAS ESR (Ankylosing Spondylitis Disease Activity Score) index (14). Additionally, the Spanish version of the BASFI (Bath Ankylosing Spondylitis Functional Index) was performed.

Measurement of ADL concentrations and anti-ADL antibodies

In all patients, a 5 mL serum sample was obtained just before subcutaneous (SC) injection of ADL and was stored at -80°C until the time of analysis. Serum concentrations of free ADL (trough level) and anti-ADL antibodies were measured using Promonitor-ADL and Promonitor Anti-ADL ELISA kits (Progenika Grifols SA, Spain). As standardised conditions, specified by the manufacturer, cut-off values were >0.024 mg/L for the serum levels of ADL and >3.5 AU/mL for positive anti-ADL antibodies. Samples with an ADL trough level <3 mg/L were considered subtherapeutic and were analysed for the presence of anti-ADL antibodies. When negative, an acid dissociation pre-treatment protocol was used, which allows for the detection of antibodies in the presence of antigen in serum, when possible drug-antibody complexes are disaggregated (15).

Statistical analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables with normal distribution of data as mean and standard deviation (SD). The chi-square (χ^2) test and the Student's *t*-test were used for comparison of qualitative and quantitative variables, respectively. Statistical significance was set at $p<0.05$.

Results

Overall population characteristics

Of the 62 patients with AS receiving ADL, 57 patients with BMI results were included. Mean (SD) BMI was 27.64 (4.36); 37 (65%) were male, and mean age was 47 (10) years. The mean progression time for the AS was 9.76 (9.33) years. The HLA-B27 was positive in 77% of patients. Fourteen (25%) patients received some DMARD in combination (methotrexate: 10, sulfasalazine: 3, azathioprine: 1). In 39 patients (68%), ADL was the primary anti-TNF used. The mean ADL treatment time was 1.44 (1.31) years. The mean blood level of ADL was 8.73 (5.69) mg/L. ADA was detected in 18 patients (32%). The mean BASDAI, BASFI and ASDAS was 4.05 (2.14), 3.9 (2.26), and 2.36 (1.26), respectively (Table I).

Characteristics based on BMI results

When comparing the patients with BMI <25 kg/m^2 (normal weight) to those with BMI >30 kg/m^2 (obese), obese patients presented significantly lower blood ADL levels (5.0 [5.52] *vs*. 9.14 [4.3], $p=0.032$), higher BASFI (4.96 [2.03] *vs*. 3.05 [1.97]; $p=0.02$) and ASDAS results (2.58 [0.79] *vs*. 1.9 [0.83]; $p=0.03$). Although it was not significant, obese patients also had a shorter ADL treatment time (1.01 [0.84] *vs*. 1.85 [1.65]; $p=0.08$) and increased BASDAI results (5.04 [2.5] *vs*. 3.5 [1.88]; $p=0.06$). However, when comparing patients with BMI between 25-30 kg/m^2 (overweight) to patients with BMI >30 kg/m^2, obese patients only presented significantly lower blood ADL levels (5.0 [5.52] *vs*. 10.09 [5.92]; $p<0.01$) (Table I).

Furthermore, the mean BMI was significantly lower among patients with a mean BASDAI ≤4 *versus* patients with BASDAI >4 (25.73[4.41] *vs*. 29.29 [3.93]; $p=0.002$), and among patients with ASDAS ≤2.1 *versus* ASDAS >2.1 (25.91 [4.42] *vs*. 29.53 [4.44]; $p<0.001$). However, no significant differences were found in the presence of anti-ADL antibodies ($p=0.13$) or concomitant DMARDs ($p=0.46$) (Fig. 1).

Lastly, obese patients showed a decreased probability of clinical response to ADL *versus* non-obese patients, achieving BASDAI ≤4 (OR: 3.5, 95%CI: 0.84–17.19; $p=0.05$) or ASDAS ≤2.1 (OR: 4.64, 95%CI: 1.02–24.13; $p=0.02$).

Discussion

Obesity can affect the response to anti-TNF drugs, like their distribution, pharmacokinetics, and serum levels. The inverse relationship of the serum level of an anti-TNF drug and efficacy is clearly established in RA (9) and AS (10). Decision algorithms have been designed based on the drug levels achieved, especially for switching or for dose reduction (9). Therefore, it is reasonable to assume a negative relationship between obesity and the serum levels of anti-TNF drugs, which could affect the drug efficacy.

In this study conducted in a clinical practice setting, obese patients presented significantly lower serum ADL levels and decreased clinical response versus non-obese patients. This is not related to the increased presence of immunogenicity in obese patients. In our study, although the prevalence of ADA was 32% and no differences were found between groups, this was similar to

Table I. Patient characteristics based on BMI results.

	Overall (n=57 / 100%)	BMI <25 (n=17 / 30%)	*p*-value <25 *vs.* >30	BMI 25-30 (n=25 / 44%)	*p*-value 25-30 *vs.* >30	BMI >30 (n=15 / 26%)
Age (years):						
mean (SD)	47.14 (10.38)	44.35 (10.12)	0.27	48.32 (12.27)	0.57	50.13 (8.06)
median	48	43		49		48
Male, n (%)	37 (65)	6 (35)	0.27	24 (60)	0.54	7 (47)
BMI, kg/m^2: mean (SD)	27.64 (4.36)	22.3 (2.14)	-	27.67 (1.33)	-	32.67 (2.06)
median	27.91	22.49		27.7		32.27
Disease progression time (years):						
mean (SD)	9.76 (9.33)	7.9 (8.73)	0.55	9.56 (8.74)	0.50	11.82 (10.86)
median	5.75	3.91		6		8.12
HLA B27 positive (%)	44 (77)	11 (65)	0.22	21 (84)	0.77	12 (80)
ADL introduction order, n (%):						
First anti-TNF (naive)	39 (68)	10 (59)	0.34	19 (76)	0.60	10 (67)
Treatment with DMARDs, n (%)	14 (25)	3 (18)	0.64	8 (32)	0.87	3 (27)
Time (years) on ADL:						
mean (SD)	1.44 (1.31)	1.85 (1.65)	**0.084**	1.46 (1.27)	0.18	1.01 (0.84)
median	1.0	1.25		1.0		1.02
No. ADL level determinations, n (%)	128	34 (27)	-	72 (56)		22 (17)
ADL level, mg/dL:						
mean (SD)	8.73 (5.69)	9.14 (4.30)	**0.032**	10.09 (5.92)	0.011	5.0 (5.52)
median	9.21	9.19		11.1		3.41
Anti-ADL antibodies, U/L, n (%):	18 (32)	3 (18)	0.39	8 (32)	0.55	7 (47)
BASDAI:						
mean (SD)	4.05 (2.14)	3.5 (1.88)	**0.069**	3.95 (2.02)	0.16	5.04 (2.50)
median	4.05	3.3		4.2		6
BASFI:						
mean (SD)	3.9 (2.26)	3.05 (1.97)	**0.023**	4.08 (2.36)	0.22	4.96 (2.03)
median	4.05	2.4		4.5		5.6
ASDAS:						
mean (SD)	2.36 (1.26)	1.9 (0.83)	**0.031**	2.24 (1.63)	0.38	2.58 (0.79)
median	2.1	1.9		2		2.65

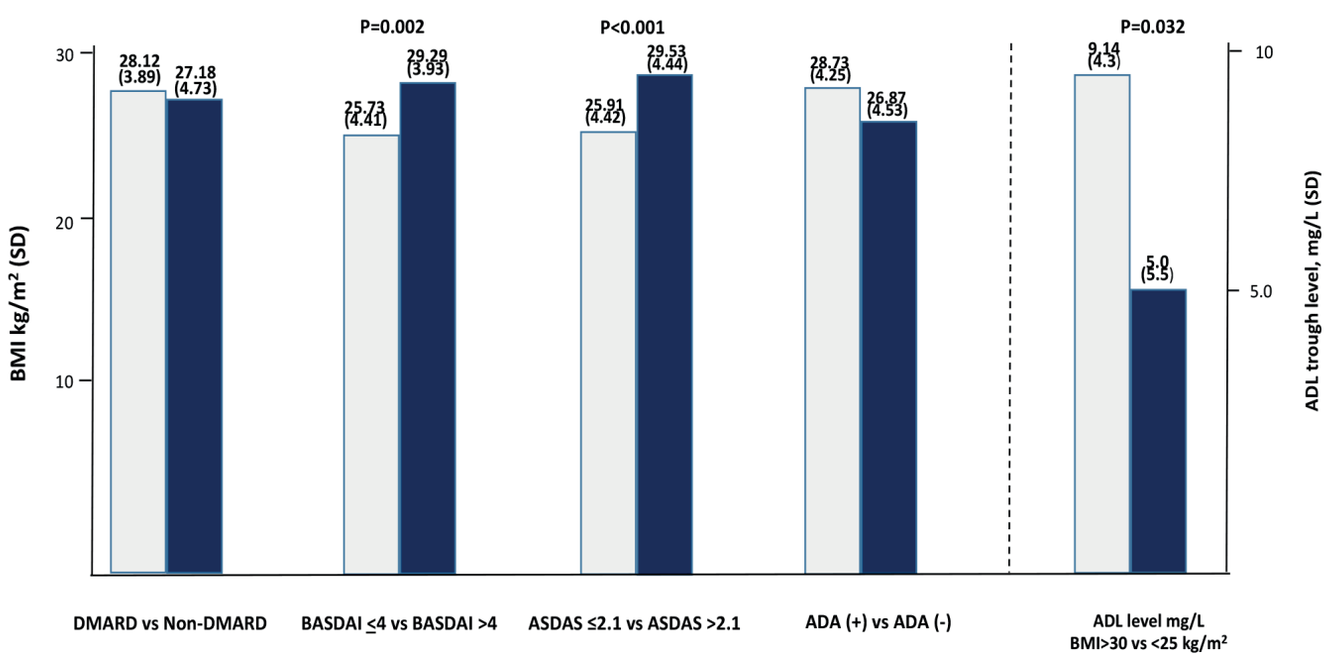

Fig. 1. BMI-based differences in patients with ankylosing spondylitis by DMARD combination, BASDAI results, ASDAS results, presence of anti-adalimumab antibodies, and adalimumab serum levels, for patients with BMI <25 kg/m^2 and >30 kg/m^2. ADA: anti-adalimumab antibody; BMI: body mass index.

other studies with AS treated with ADL (10). Moreover, 14 patients (25%) received a DMARD, in 10 (17%) of them methotrexate. This immunogenicity result is greater than the 7% reported in a study in which all patients with RA treated with ADL received a DMARD (9).

Few studies analyse the relationship between BMI and clinical response in patients with AS treated with anti-TNFs. As in our study, in most patients the increase in BMI or obesity is related to the decreased efficacy of anti-TNF.

In the study by Ottaviani *et al*. (16), of 155 patients with AS receiving infliximab (INF), at 6 months, patients with increased BMI showed significantly worse clinical response in BASDAI-50.

In the study by Simone *et al*. (17), of 153 patients with AS receiving anti-TNF, being female and having an elevated BMI were related to the decreased probability of clinical efficacy (OR 40, 95%CI; 4.2- 333.3).

In the study by Gremese *et al*. (18) of 170 patients with AS receiving INF, ADL or etanercept, patients with increased BMI achieved worse clinical response (p=0.002), and the strongest independent predictor for not achieving response, by BASDAI-50 at 12 months was a BMI >30 kg/m^2 (OR 3.57 95% CI: 1.15–11.11). However, in patients treated with ADL or etanercept, the mean BASDAI-50 was greater in non-obese patients, although non-significant, as opposed to patients treated with INF. In our study, in obese patients mean BASDAI was greater but not significant, although the measurement with ASDAS was significant.

Our study does have limitations. It is a cross-sectional study, although the most important factor is the sample size, which could affect the results. However, the data represents clinical practice.

BMI and weight, are modifiable factors with negative influence, it would be advisable to inform patients for better disease control. However, more studies are needed to appropriately evaluate this aspect.

In conclusion, in patients with AS receiving ADL, obese patients have significantly lower serum ADL levels and decreased clinical response, without an increase in immunogenicity.

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