Influence of obesity and gender on drug effectiveness in rheumatoid arthritis depends on the outcome considered

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Conclusions

Depending on the considered outcome, the influence of obesity on drug effectiveness is mediated by gender to some extent. Obesity negatively influences the effectiveness in particular of those biologics that target single cytokines, i.e., tumor necrosis factor inhibitors and tocilizumab, while therapies targeting specific immune cell populations are only marginally affected.
In tocilizumab, the effect of obesity might be attenuated by a better weight adjustment of its dosage.

Background & Objectives

Obesity in patients with rheumatoid arthritis (RA) affects effectiveness of tumor necrosis factor inhibitors (TNFi), but not abatacept and rituximab. For tocilizumab (TOC), the situation is unclear. It also remains unresolved whether gender acts as an effect modifier. The objective was to assess how obesity impacts response to common DMARDs, considering potential differences between sexes.

Patients & Methods

The German biologics register RABBIT continuously includes RA patients with a new DMARD start after at least one csDMARD failure. Among patients enrolled between 01/2009 and 10/2017 (n=9,455), patients with BMI ≥ 18.5 and ≥ 6 months of follow-up were selected (n=9,245). Effectiveness was measured as the improvement of DAS28-CRP and its components during the first 6 months of treatment.

(I) The obesity effect was assessed by linear regression, adjusting for age, baseline outcome value, disease duration, prior bDMARD failure, glucocorticoid dosage, number of comorbidities, erosions, seropositivity, and smoking habits. Missing values were addressed by multiple imputations. CRP levels were log-transformed.

(II) To assess whether patients received norm dosage, a tolerance interval was defined for TOC and infliximab (INF) (≤ 15% underdosage, ≤ 15% (TOC) or ≤ 50% (INF) overdosage considered as norm).

	Normal weight (18.5 ≤ BMI < 25)		Overweight (25 ≤ BMI < 30)		Obesity (BMI ≥ 30)	
Table: Baseline characteristics of patients in BMI/gender groups	Women n=2716 (80.2%)	Men n=670 (19.8%)	Women n=2239 (67.1%)	Men n=1100 (32.9%)	Women n=1895 (75.2%)	Men n=625 (24.8%)
Age in years	55.6 ± 13.8	57.7 ± 13.5	59.3 ± 12.2	58.6 ± 11.4	58.1 ± 11.6	57.1 ± 10.6
DAS28-CRP	4.3 ± 1.2	4.4 ± 1.2	4.4 ± 1.1	4.5 ± 1.2	4.6 ± 1.1	4.5 ± 1.2
Swollen joints count (SJC)	5.1 ± 4.6	5.3 ± 5	5.1 ± 4.6	5.2 ± 4.9	5.2 ± 4.8	5.1 ± 4.7
Tender joints count (TJC)	7.1 ± 6.2	7 ± 6.4	7.9 ± 6.6	7.3 ± 6.4	8.4 ± 6.8	7.7 ± 6.9
Patient global health asessment	5.5 ± 2.1	5.4 ± 2.1	5.8 ± 2.1	5.7 ± 2.1	6.1 ± 2	5.8 ± 2.1
C-reactive protein (CRP) in mg/l	11.7 ± 18.8	18.5 ± 24.7	11.7 ± 16.3	17 ± 23.7	13.2 ± 16.2	15.5 ± 19.4
% of full physical funcion	69.9 ± 22	74.4 ± 21	64 ± 22.4	72.4 ± 21.8	58.2 ± 22.5	67.9 ± 23
Sum of comorbidities	1.7 ± 1.9	1.8 ± 2.1	2.3 ± 2.2	2.2 ± 2.2	2.8 ± 2.3	2.6 ± 2.3
Ever smoked	1334 (49.1%)	475 (70.9%)	988 (44.1%)	844 (76.7%)	881 (46.5%)	469 (75%)
Disease duration in years	10.1 ± 9.1	7.8 ± 8.2	10 ± 9.2	7.3 ± 7.4	8.7 ± 8.4	6.3 ± 6.5
Joint erosions	1447 (55.2%)	330.0 (51.3%)	1085 (51.1%)	483.0 (46.4%)	697.0 (39.2%)	247.0 (41.2%)
Seropositivity (RF or anti-CCP)	2119.8 (78%)	504.9 (75.4%)	1620.7 (72.4%)	8183 (74.4%)	1244.6 (65.7%)	429.8 (68.8%)
Glucocorticoid therapy (last 6 months)	1552 (57.1%)	412 (61.5%)	1323 (59.1%)	646 (58.7%)	1103 (58.2%)	357 (57.1%)

Results

Patient characteristics (see table)

- Obese RA patients were comparable to non-obese patients in age (both mean 58 years) and gender (women: 75% vs. 74%) at baseline. They were less frequently seropositive (66% vs. 75%), less likely to have joint erosions (40% vs. 52%), but more likely to have ≥ 3 comorbidities (45% vs. 30%).
- Women had worse physical abilities than men (65% vs. 72 % of full physical function), particularly among obese patients (58% vs. 68 %). They were more likely to have a DAS28-CRP ≥ 5.1 (50% vs. 41%), but had smaller overall CRP values (mean 12 vs. 17 mg/l) and were less likely to ever smoke than men (47% vs. 75%).

Dosage

- 95% of treatments were dosed as recommended, at least ~ 90% for any particular therapy, also among obese patients (exception: only 78% norm dosage for INF).
- TOC underdosage had a significant negative effect on SJC improvement. TOC patients tended to show weight gains, which correlated negatively with change in dosis/kg weight.

Effect of obesity (see figure)

- Among women receiving TNFi, a significant negative effect of obesity on the improvement of CRP levels after 6 months of treatment was observed. The effect in men differed significantly (see circle), possibly influenced by gender specific body fat distributions.
- For women under TNFi or csDMARDs, obesity significantly affected DAS28-CRP improvement. Such an effect was also observed for TOC, unlike in past studies.

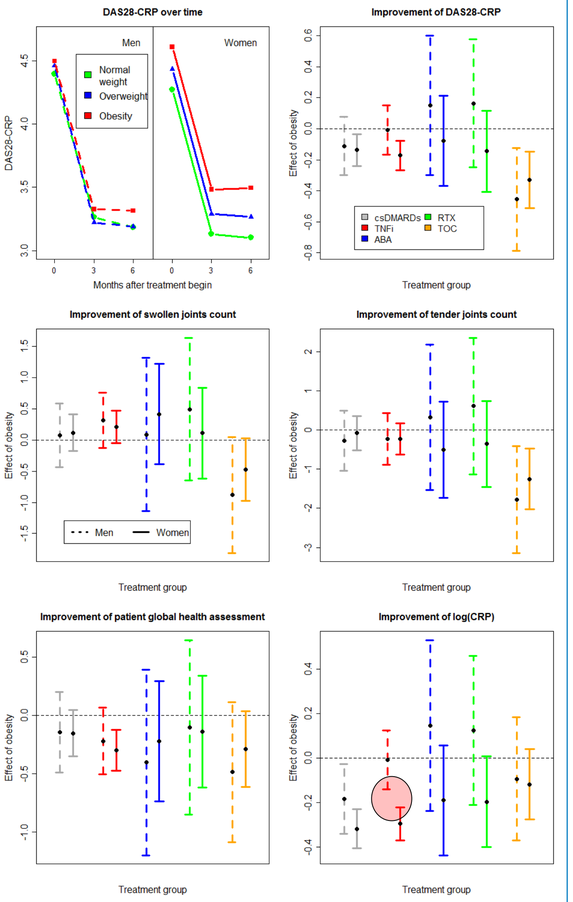

Figure: Adjusted effects of obesity for groups defined by gender and therapy mechanism of action

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