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Comparative effectiveness of biologics in patients with rheumatoid arthritis stratified by body mass index: a cohort study in a Swiss registry

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ABSTRACT

Objectives Obesity is associated with lower treatment response in patients with rheumatoid arthritis (RA). In patients with obesity, abatacept was suggested as a preferable option to tumour necrosis factor-alpha inhibitors. We aimed to assess the comparative effectiveness of etanercept, infliximab and abatacept, compared with adalimumab, in patients with RA with obesity. Secondarily, we also investigated this in patients with overweight and normal weight for completeness.

Design Observational cohort study.

Setting Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) registry (1997–2019).

Participants Adult patients with RA from the SCQM registry who received etanercept, infliximab, abatacept or adalimumab as their first biological or targeted synthetic disease-modifying antirheumatic drug were classified based on their body mass index (BMI) at the start of that treatment in three cohorts: obese, overweight, normal weight. They were followed for a maximum of 1 year.

Exposure The study exposure of interest was the patients' first biological, particularly: etanercept, infliximab and abatacept, compared with adalimumab.

Primary and secondary outcome measures The primary study outcome was remission within 12 months, defined as 28-joint Disease Activity Score (DAS28) <2.6. Missingness was addressed using confounder-adjusted response rate with attrition correction. Logistic regression was used to compare the effectiveness of etanercept, infliximab and abatacept versus adalimumab. Each BMI cohort was addressed and analysed separately.

Results The study included 443 obese, 829 overweight and 1243 normal weight patients with RA. There were no statistically significant differences in the odds of DAS28-remission at ≤12 months for etanercept, infliximab and abatacept, compared with adalimumab, in any of the BMI cohorts.

Conclusions No differences in DAS28-remission were found between the study drugs and adalimumab as first biologic in patients with RA, independently of the BMI cohort. We did not find evidence that treatment with abatacept increased the likelihood of remission compared with adalimumab among obese patients with RA.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ While stratifying by body mass index (BMI) reduces the sample size (reducing study power), it enables to study rheumatoid arthritis patients without the bias that BMI-driven differences could impact on.
⇒ This study investigated only four biologics and, although investigating other biologics is of interest, this was not feasible due to their limited sample size.
⇒ This study used confounder-adjusted response rate with attrition correction to deal with missingness.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease, primarily characterised by joint damage, which can lead to disability.[1 2] Its pathogenesis and clinical presentation may vary between individuals and disease stages.[1] Following failure to achieve the therapeutic target with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), the European Alliance of Associations for Rheumatology (EULAR) recommends adding a biological or targeted synthetic disease-modifying anti-rheumatic drug (b/tsDMARD).[3] Supported by a recent systematic review,[4] the current EULAR guidelines have no preference for specific b/tsDMARD due to similar efficacy.[3]

Despite the advances in the treatment of RA and the availability of several b/tsDMARDs, up to 60% of patients will either not respond or lose response to therapy over time.[5–8] Thus, evidence-based decision on the optimal b/tsDMARD for each patient remains challenging. This is specifically important for patients with RA with high body mass index (BMI) since obesity has been associated with worse disease activity and disease management in patients with RA,[9–14] and the prevalence of

obesity was reported higher among RA cohorts compared with the reference populations.[15 16] There are hypotheses to explain the reduced therapeutic response in patients with obesity. First, obesity is a low-grade systemic inflammatory condition,[17] which may share a common pathological pathway with immune-mediated diseases. Second, body weight can affect the drug's volume of distribution.[18] Third, the probability of developing antidrug antibodies (ADAbs) increases with higher body weight.[19] And fourth, obesity may affect and be affected by socially constructed norms and behaviours with an impact on clinical management (eg, weight stigma associated with less exercise[20]).

While previous studies have shown that obesity is associated with a detrimental response to tumour necrosis factor-alpha (TNF) inhibitors,[10 14 21] it has been suggested that high BMI does not influence the response to the non-TNF biological abatacept.[22–24] However, these studies assessed the impact of obesity on the treatment response solely among users of abatacept,[22–24] and often had small sample sizes.[22 24] Thus, it remains of interest to study the comparative effectiveness of TNF inhibitors versus abatacept in patients with RA with obesity. Additionally, although similar effectiveness was suggested across TNF inhibitors in the general RA population,[25] it is unclear if this is the case in every BMI group.

We performed a comparative effectiveness analysis among patients with RA with obesity who were new users of biologics in the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) database. Secondarily, we also investigated this among patients with RA with overweight, as well as patients with RA with normal weight, for completeness.

METHODS

Data source and study design

This is an observational cohort study in the SCQM[26] registry from 1 January 1997 to 31 July 2019. The SCQM includes routinely collected data from rheumatology visits and patient-reported outcomes, including patient demographics, lifestyle habits, clinical endpoints, antirheumatic medication (with start and stop dates), patient-reported outcomes and health standardised surveys.[16] More details have been described elsewhere.[16]

Study population

The study included adult (>18 years) patients with RA registered in SCQM, who started adalimumab, etanercept, infliximab or abatacept as their first b/tsDMARD between 1 January 1997 and 31 July 2018. Patients were stratified by BMI category at the start of treatment (index date). BMI categories were obese (BMI≥30 kg/m^2), overweight (≥25 and <30 kg/m^2) and normal weight (BMI≥18.5 and <25 kg/m^2). Each BMI group was studied separately, as independent cohorts. We excluded patients without a baseline BMI record and underweight patients (BMI<18.5 kg/m^2).

The primary cohort of interest was the obese cohort, but we similarly investigated the overweight and normal weight cohorts for completeness, to provide more holistic evidence.

Exposure

The study exposure was the patient's first b/tsDMARD, including etanercept, infliximab and abatacept, compared with adalimumab.

Outcome and follow-up

The primary outcome was clinical response during the treatment course with a maximum follow-up of 12 months. Clinical response was primarily defined as 28-joint Disease Activity Score (DAS28) remission (DAS28<2.6), which was calculated using the erythrocyte sedimentation rate (ESR, DAS28-ESR). Secondarily, clinical response was also assessed as DAS28 low disease activity (LDA), defined as DAS28<3.2; and Rheumatoid Arthritis Disease Activity Index-Five (RADAI-5) remission, defined as RADAI-5≤1.4. One record of achieved outcome during follow-up (ie, treatment course with a maximum of 12 months) was considered sufficient to qualify for the corresponding achieved outcome. Treatment course was assessed using drug-specific extended time-windows after treatment stop. These were 42 days for adalimumab, 30 days for etanercept, 90 days for infliximab and 60 or 30 days for intravenous and subcutaneous abatacept, respectively. Additionally, a permissible gap of up to 1 month between stop and restart of the same treatment was accepted as treatment continuation. A schematic representation of the follow-up for the primary outcome can be seen in online supplemental figure S1, also including details regarding the drug-specific extended time-windows included as follow-up after record of treatment stop.

Additional secondary outcomes were the median change (Δ, delta) in unidimensional parameters between baseline and the best respective measurement during follow-up as described above. These included ΔESR, delta C reactive protein (ΔCRP), delta tender joint counts (ΔTJC28) and delta swollen joint counts (ΔSJC28). Here, median values <0 reflect improvement and reduction of the respective values.

Following recent recommendations from EULAR,[27 28] missing information on primary and secondary outcomes was addressed using the confounder-adjusted response rate with attrition correction (CARRAC).[28] This consisted of multiple imputation by chain equation that included baseline variables, treatment duration and reason for treatment discontinuation. Additionally, missingness for the clinical response outcomes was also addressed in two other manners as sensitivity analyses: first, assuming that lack of information on outcome during follow-up was equivalent to not-achieving the outcome (MOIAN, Missing Outcome Information Assumed as No); and second, excluding patients who miss this information on outcome during follow-up (EPMOI, Excluding Patients Missing Outcome Information).

The tertiary outcome was treatment survival with a maximum follow-up of 5 years, overall and stratified by the reason for treatment stop adverse event(s) or remission, as recorded by the clinician. For this, we used the record of treatment stop without additional time extension and accepted ≤1 month gaps between stop and restart of the same biologic as treatment continuation. Treatment stop was defined by a record of stop or by the start of a new b/tsDMARD. Otherwise, patients were censored at the time of stopping their participation at SCQM, at the end of the study period (31 July 2019), or 3 months after a visit with no subsequent visits for >2 years.

Covariates

Patient baseline characteristics were collected at the index date or within predefined look-back windows. Information on patient demographics, disease duration (time from RA diagnosis), seropositivity, swollen and tender joint counts (SJC28, TJC28), physician global disease activity (GDA) and body weight was collected within the 6 months prior index date. Inflammatory markers (ESR, CRP), disease activity score (DAS) and the Health Assessment Questionnaire (HAQ) were collected within the 3 months prior index date. Information on smoking (ever smoker), body height and comorbidities was collected with an ever-before look-back window, except for records on fractures/surgeries/musculoskeletal system, which were collected within the 6 months prior index date. Information on pregnancy or breast feeding was collected with a 12-month look-back window. Information on rheumatic medication was collected at the index date, including csDMARD use, steroid use and type of b/tsDMARD.

Statistical analysis

The obese, overweight and normal weight groups were addressed as three distinctive cohorts. Patient baseline characteristics for each study cohort were described stratified by the exposure drug. The etanercept, infliximab and abatacept groups were compared with the adalimumab group using χ^2 test for categorical variables and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

CARRAC was performed prior to the analysis of the clinical response outcomes and the change in unidimensional parameters. We performed 60 imputations on an outcome and cohort basis (ie, this means that we conducted CARRAC separately for each cohort and each respective outcomes). We visually assessed the convergence of the imputations by mean and variance changes and addressed the overlapping of the distribution of continuous variables with density plots. Information on included variables and methods used in the imputations is described in online supplemental table S1. All variables to be used in the analyses were included in the imputation models. An example of visual assessment of the imputation of DAS28-ESR for the primary outcome (DAS28-remission) is depicted in online supplemental figure S2.

Comparative effectiveness of the study drugs for the clinical response outcomes was assessed using logistic regression, with adalimumab as the reference group. Following the CARRAC, logistic regression was performed in each imputed dataset, and the results were subsequently pooled into a single estimate according to Rubin's rules. This regression was conducted, first, adjusting for age and sex, and second, adjusting for age, sex, index year, baseline DAS28, csDMARD at index, and steroid use at index. Sensitivity analyses were performed by MOIAN and EPMOI, followed by logistic regression calculating age-adjusted and sex-adjusted odds ratio (OR).

Change in individual parameters (ΔESR, ΔCRP, ΔTJC28, ΔSJC28) was described using the median and interquartile range (IQR) and the Kruskal-Wallis test compared between the exposure drugs, using adalimumab as reference. Lastly, treatment survival was investigated with Kaplan-Meier curves for each cohort overall and stratified by reason of treatment stop (adverse event(s); remission) as recorded by the clinician. Treatment survival across drugs was compared using the log-rank test.

All analyses were independently (separately) performed for each BMI cohort (obese, overweight and normal weight).

The statistical analyses were performed with the R software, V.3.5.2.[29]

Patient and public involvement

A patient was involved in the study conceptualisation, methodology and interpretation of the findings, as well as approval of the final manuscript.

RESULTS

The study included 2515 patients with RA, among whom 443 (17.6%), 829 (33.0%) and 1243 (49.4%) were included in the obese, overweight and normal weight cohorts, respectively (online supplemental figure S3). The most commonly prescribed drugs were adalimumab and etanercept.

Baseline characteristics for the obese cohort, overweight and normal weight cohorts are described in table 1, and additional information (eg, missingness) is provided in online supplemental tables S3–S5. In every BMI cohort, the median year of index date generally differed between the study drugs, with infliximab having the earliest and abatacept the latest. Etanercept users were very similar to adalimumab users in all BMI categories but had a significantly lower percentage of csDMARD use at index date in the obese and normal weight cohorts. Compared with the adalimumab group, infliximab users had significantly more frequent use of prednisone at index in every BMI cohort, significantly more frequent use of csDMARD at index, worse HAQ, and more frequent depression/anxiety in the overweight and normal weight cohorts. In comparison to the adalimumab group, abatacept users

Table 1 Patient characteristics at baseline, stratified by first b/tsDMARD adalimumab, etanercept, infliximab and abatacept in the obese, overweight and normal weight cohorts

	Adalimumab	Etanercept		Infliximab		Abatacept	
Obese cohort	**(n=178)**	**(n=150)**	**P value**	**(n=73)**	**P value**	**(n=42)**	**P value**
Women (%)	130 (73.0)	124 (82.7)	0.052	56 (76.7)	0.656	27 (64.3)	0.348
Age index (mean (SD))	56.60 (11.99)	56.98 (11.63)	0.777	55.86 (10.77)	0.644	59.27 (10.00)	0.183
RA duration, years (mean (SD))	6.72 (8.67)	7.75 (8.45)	0.285	7.92 (8.61)	0.331	5.80 (7.42)	0.531
Year of index date (mean (SD))	2007.85 (3.79)	2007.53 (4.56)	0.487	2005.68 (4.02)	<0.001	2013.19 (2.52)	<0.001
BMI kg/m^2 (mean (SD))	33.90 (3.86)	33.79 (3.85)	0.794	33.65 (3.09)	0.621	33.91 (3.99)	0.987
Ever smoker (%)	49 (27.5)	41 (27.3)	1.000	11 (15.1)	0.053	22 (52.4)	0.004
csDMARD at index date (%)	134 (75.3)	96 (64.0)	0.036	60 (82.2)	0.307	33 (78.6)	0.804
Prednisone at index date (%)	66 (37.1)	60 (40.0)	0.669	41 (56.2)	0.008	18 (42.9)	0.605
Seropositive* (%)	129 (72.5)	102 (68.0)	0.691	56 (76.7)	0.537	32 (76.2)	0.765
ESR (mean (SD))	24.22 (18.46)	23.73 (16.09)	0.809	29.43 (18.87)	0.053	22.00 (18.05)	0.518
CRP (mean (SD))	1.44 (1.20)	1.37 (1.42)	0.765	1.38 (1.08)	0.842	1.06 (0.97)	0.106
Tender joint counts 28 (mean (SD))	7.25 (6.92)	7.86 (6.75)	0.432	8.14 (7.20)	0.367	7.19 (6.66)	0.963
Swollen joint counts 28 (mean (SD))	6.75 (5.72)	6.63 (5.79)	0.865	7.38 (6.37)	0.449	5.73 (4.85)	0.317
Physician GDA (mean (SD))	4.94 (1.85)	4.93 (1.95)	0.950	5.29 (2.13)	0.344	4.09 (1.99)	0.024
DAS28-ESR (mean (SD))	4.40 (1.42)	4.54 (1.32)	0.406	4.72 (1.40)	0.118	4.18 (1.46)	0.399
RADAI-5 (mean (SD))	4.91 (2.04)	5.33 (2.18)	0.107	5.15 (2.12)	0.425	4.35 (2.36)	0.209
HAQ (mean (SD))	1.21 (0.74)	1.32 (0.73)	0.235	1.38 (0.77)	0.115	0.95 (0.70)	0.093
Osteoporosis†	24 (13.5)	23 (15.3)	0.750	11 (15.1)	0.898	4 (9.5)	0.663
Other rheumatological disease(s)‡	61 (34.3)	62 (41.3)	0.229	25 (34.2)	1.000	8 (19.0)	0.084
Psoriasis	<5	<5	NA	<5	NA	<5	NA
Hyperlipidaemia	15 (8.4)	11 (7.3)	0.873	5 (6.8)	0.871	10 (23.8)	0.011
Cardiac/cardiovascular event/disease§	84 (47.2)	84 (56.0)	0.139	32 (43.8)	0.730	30 (71.4)	0.008
Depression/anxiety¶	25 (14.0)	31 (20.7)	0.150	12 (16.4)	0.772	7 (16.7)	0.849
Diabetes	17 (9.6)	23 (15.3)	0.154	9 (12.3)	0.669	8 (19.0)	0.140
Fractures, surgeries, musculoskeletal system	15 (8.4)	8 (5.3)	0.381	7 (9.6)	0.960	<5	NA
Overweight cohort	**(n=336)**	**(n=296)**	**P value**	**(n=150)**	**P value**	**(n=47)**	**P value**
Women (%)	215 (64.0)	203 (68.6)	0.257	91 (60.7)	0.549	30 (63.8)	1.000
Age index (mean (SD))	57.28 (12.52)	57.81 (12.32)	0.589	56.87 (11.35)	0.734	62.99 (10.81)	0.003
RA duration, years (mean (SD))	7.10 (7.76)	8.45 (9.21)	0.050	7.66 (8.08)	0.477	6.60 (8.45)	0.690
Year of index date (mean (SD))	2007.68 (3.56)	2006.72 (5.02)	0.005	2005.93 (4.69)	<0.001	2012.32 (2.60)	<0.001
BMI kg/m^2 (mean (SD))	27.16 (1.35)	27.21 (1.33)	0.643	27.13 (1.37)	0.829	27.19 (1.41)	0.885
Ever smoker (%)	94 (28.0)	76 (25.7)	0.575	43 (28.7)	0.962	22 (46.8)	0.014
csDMARD at index date (%)	226 (67.3)	189 (63.9)	0.414	126 (84.0)	<0.001	34 (72.3)	0.595
Prednisone at index date (%)	134 (39.9)	133 (44.9)	0.229	84 (56.0)	0.001	13 (27.7)	0.146
Seropositive* (%)	244 (72.6)	211 (71.3)	0.679	119 (79.3)	0.731	37 (78.7)	0.697
ESR (mean (SD))	24.82 (19.57)	25.87 (22.59)	0.555	25.44 (21.41)	0.766	28.92 (18.07)	0.221
CRP (mean (SD))	2.12 (3.25)	1.71 (3.10)	0.315	1.18 (1.68)	0.057	1.30 (1.48)	0.121
Tender joint counts 28 (mean (SD))	7.55 (6.90)	7.95 (7.69)	0.507	7.14 (6.85)	0.552	6.00 (5.88)	0.161
Swollen joint counts 28 (mean (SD))	6.90 (5.51)	6.68 (5.93)	0.639	7.92 (5.98)	0.077	5.82 (5.18)	0.219
Physician GDA (mean (SD))	4.92 (2.27)	4.90 (2.14)	0.907	5.56 (2.04)	0.033	4.28 (1.89)	0.091
DAS28-ESR (mean (SD))	4.47 (1.34)	4.42 (1.50)	0.690	4.42 (1.48)	0.747	4.49 (1.15)	0.933
RADAI-5 (mean (SD))	4.84 (2.08)	5.01 (2.17)	0.358	4.98 (2.18)	0.528	4.87 (2.35)	0.935
HAQ (mean (SD))	1.08 (0.70)	1.13 (0.74)	0.408	1.24 (0.72)	0.030	0.94 (0.69)	0.272
Osteoporosis†	59 (17.6)	61 (20.6)	0.382	33 (22.0)	0.303	11 (23.4)	0.442
Other rheumatological disease(s)‡	101 (30.1)	97 (32.8)	0.517	45 (30.0)	1.000	13 (27.7)	0.868
Psoriasis	<5	<5	NA	<5	NA	<5	NA
Hyperlipidaemia	16 (4.8)	25 (8.4)	0.086	8 (5.3)	0.967	7 (14.9)	0.016

Continued

Table 1 Continued

	Adalimumab	Etanercept		Infliximab		Abatacept	
Cardiac/cardiovascular event/disease§	123 (36.6)	117 (39.5)	0.501	58 (38.7)	0.740	21 (44.7)	0.363
Depression/anxiety¶	31 (9.2)	42 (14.2)	0.068	27 (18.0)	0.009	<5	NA
Diabetes	26 (7.7)	19 (6.4)	0.625	8 (5.3)	0.443	8 (17.0)	0.068
Fractures, surgeries, musculoskeletal system	26 (7.7)	34 (11.5)	0.142	13 (8.7)	0.867	<5	NA
Normal weight cohort	**(n=442)**	**(n=482)**	**P value**	**(n=259)**	**P value**	**(n=60)**	**P value**
Women (%)	365 (82.6)	393 (81.5)	0.744	207 (79.9)	0.438	51 (85.0)	0.776
Age index (mean (SD))	53.24 (13.78)	54.32 (14.68)	0.253	53.15 (14.28)	0.936	61.97 (14.34)	<0.001
RA duration, years (mean (SD))	8.29 (9.16)	8.66 (8.96)	0.537	9.82 (9.32)	0.036	9.15 (10.51)	0.506
Year of index date (mean (SD))	2007.33 (3.46)	2005.82 (4.90)	<0.001	2004.81 (4.04)	<0.001	2012.72 (2.68)	<0.001
BMI kg/m^2 (mean (SD))	22.17 (1.77)	22.07 (1.82)	0.413	22.17 (1.82)	0.973	22.43 (1.74)	0.278
Ever smoker (%)	122 (27.6)	119 (24.7)	0.351	55 (21.2)	0.075	18 (30.0)	0.814
csDMARD at index date (%)	316 (71.5)	265 (55.0)	<0.001	208 (80.3)	0.012	38 (63.3)	0.250
Prednisone at index date (%)	168 (38.0)	193 (40.0)	0.572	124 (47.9)	0.013	27 (45.0)	0.367
Seropositive (%)	325 (73.5)	379 (78.6)	0.175	208 (80.3)	0.012	46 (76.7)	0.456
ESR (mean (SD))	23.49 (20.10)	25.78 (23.17)	0.134	26.11 (24.61)	0.149	26.87 (22.18)	0.288
CRP (mean (SD))	1.28 (1.57)	1.32 (1.61)	0.855	1.44 (1.98)	0.561	1.47 (1.92)	0.506
Tender joint counts 28 (mean (SD))	6.70 (6.41)	6.69 (6.66)	0.989	6.59 (6.75)	0.837	6.44 (5.59)	0.783
Swollen joint counts 28 (mean (SD))	6.56 (5.67)	6.83 (6.09)	0.506	8.42 (6.92)	<0.001	6.17 (5.31)	0.635
Physician GDA (mean (SD))	4.98 (2.12)	5.14 (2.17)	0.397	5.23 (2.18)	0.269	4.40 (1.75)	0.101
DAS28-ESR (mean (SD))	4.29 (1.40)	4.30 (1.43)	0.926	4.35 (1.57)	0.619	4.33 (1.18)	0.836
RADAI-5 (mean (SD))	4.61 (2.22)	4.69 (2.14)	0.61	4.59 (2.10)	0.888	4.34 (1.81)	0.434
HAQ (mean (SD))	0.96 (0.70)	1.03 (0.72)	0.173	1.12 (0.72)	0.010	0.78 (0.64)	0.089
Osteoporosis	88 (19.9)	101 (21.0)	0.755	61 (23.6)	0.297	23 (38.3)	0.002
Other rheumatological disease	99 (22.4)	118 (24.5)	0.504	70 (27.0)	0.197	16 (26.7)	0.566
Psoriasis	5 (1.1)	<5	NA	<5	NA	<5	NA
Hyperlipidaemia	9 (2.0)	14 (2.9)	0.525	<5	NA	7 (11.7)	<0.001
Cardiac/cardiovascular event/disease	78 (17.6)	115 (23.9)	0.025	56 (21.6)	0.233	31 (51.7)	<0.001
Depression/anxiety	30 (6.8)	46 (9.5)	0.160	30 (11.6)	0.040	6 (10.0)	0.523
Diabetes	6 (1.4)	21 (4.4)	0.012	<5	NA	<5	NA
Fractures, surgeries, musculoskeletal system	43 (9.7)	60 (12.4)	0.227	38 (14.7)	0.064	<5	NA

Values are the number and column percentage, unless otherwise specified. Significance tests compare each drug of interest to adalimumab, using $\chi 2$ test for categorical variables and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.
*Seropositivity was calculated using both rheumatoid factor and anticyclic citrullinated peptide antibodies.
†Osteoporosis includes osteoporosis record or medication with bisphosphonates, denosumab or teriparatide.
‡Other rheumatological disease includes gout, lupus, osteoarthritis, Sjogren's syndrome, degenerative spine disease, degenerative spondylopathy, other connective tissue disease and other rheumatological disease.
§Cardiac/cardiovascular event/disease includes myocardial infarction, heart infarct, heart failure, heart insufficiency, cardiac insufficiency, coronary heart disease, coronary cardiac disease, heart problem, heart disease, angina pectoris, rhythm disorder, artery intervention, stroke transient ischaemic attack, cerebrovascular disease, deep venous thrombosis, peripheral vascular disease, pulmonary embolism, blood thinners, hypertension, hypotension, other cardiovascular disease and medication with platelet aggregation inhibitors, antihypertensives or statins.
¶Depression/anxiety includes record of the disease or medication with antidepressants.
BMI, body mass index; b/tsDMARD, biological or targeted synthetic disease-modifying antirheumatic drug; CRP, C reactive protein; csDMARD, conventional synthetic DMARD; DAS28-ESR, 28-joint Disease Activity Score using erythrocyte sedimentation rate; GDA, global disease activity; HAQ, Health Assessment Questionnaire; NA, not applicable; RA, rheumatoid arthritis; RADAI-5, Rheumatoid Arthritis Disease Activity Index-Five.

were more frequently current or ever smokers in the overweight and obese cohorts and generally had more frequent history of hyperlipidaemia and cardiac/cardiovascular event/disease and a tendency for more frequent diabetes.

Table 2 provides the results from the comparative effectiveness analysis for the clinical response outcomes (DAS28-remission; DAS28-LDA; RADAI-5-remission) in the overall BMI cohorts using CARRAC and the sensitivity analysis MOIAN. The respective EPMOI sensitivity analyses are presented in online supplemental table S6. No significant differences were identified across the study drugs compared with adalimumab, independently of the BMI cohort, with only one exception: In overweight patients, etanercept was associated with a reduced odds of achieving RADAI-5 remission (ORadj 0.44, 95% CI 0.22 to 0.90).

Table 2 Comparative effectiveness analyses

			Main analyses (CARRAC)			Sensitivity analyses (MOIAN)	
		n all	n event*	OR	ORadj	n event	OR
Obese	DAS28-remission						
	adalimumab	178	57	1 (ref.)	1 (ref.)	25	1 (ref.)
	etanercept	150	48	1.01 (0.48–2.12)	1.01 (0.43–2.40)	21	1.08 (0.57–2.03)
	infliximab	73	17	0.49 (0.18–1.32)	0.77 (0.26–2.34)	7	0.66 (0.25–1.54)
	abatacept	42	16	0.91 (0.30–2.82)	0.61 (0.16–2.25)	6	0.97 (0.34–2.43)
	DAS28-LDA						
	adalimumab	178	87	1 (ref.)	1 (ref.)	37	1 (ref.)
	etanercept	150	73	0.95 (0.47–1.90)	0.77 (0.33–1.80)	32	1.05 (0.61–1.80)
	infliximab	73	31	0.85 (0.36–1.99)	1.00 (0.36–2.74)	15	1.01 (0.50–1.95)
	abatacept	42	23	0.68 (0.24–1.97)	0.72 (0.19–2.74)	8	0.84 (0.34–1.91)
	RADAI-5-remission						
	adalimumab	178	32	1 (ref.)	1 (ref.)	11	1 (ref.)
	etanercept	150	22	0.95 (0.36–2.55)	1.05 (0.32–3.51)	9	1.01 (0.39–2.52)
	infliximab	73	10	1.01 (0.31–3.28)	0.64 (0.15–2.80)	5	1.13 (0.35–3.24)
	abatacept	42	9	1.21 (0.33–4.38)	5.43 (0.96–30.87)	<5	NA
Overweight	DAS28-remission						
	adalimumab	336	111	1 (ref.)	1 (ref.)	55	1 (ref.)
	etanercept	296	93	0.83 (0.50–1.37)	0.97 (0.54–1.75)	44	0.9 (0.58–1.38)
	infliximab	150	59	1.15 (0.66–2.03)	1.77 (0.90–3.47)	33	1.45 (0.88–2.34)
	abatacept	47	18	1.18 (0.45–3.05)	0.70 (0.21–2.32)	8	1.18 (0.49–2.57)
	DAS28-LDA						
	adalimumab	336	170	1 (ref.)	1 (ref.)	84	1 (ref.)
	etanercept	296	135	0.63 (0.39–1.02)	0.83 (0.47–1.45)	62	0.79 (0.54–1.15)
	infliximab	150	80	0.89 (0.51–1.54)	1.52 (0.78–2.97)	44	1.25 (0.81–1.92)
	abatacept	47	27	1.15 (0.46–2.86)	0.98 (0.30–3.22)	13	1.22 (0.59–2.39)
	RADAI-5-remission						
	adalimumab	336	75	1 (ref.)	1 (ref.)	35	1 (ref.)
	etanercept	296	47	0.43 (0.23–0.84)	0.44 (0.22–0.90)	16	0.49 (0.26–0.90)
	infliximab	150	31	0.82 (0.42–1.57)	0.79 (0.38–1.64)	18	1.17 (0.63–2.12)
	abatacept	47	11	1.33 (0.38–4.71)	1.48 (0.32–6.79)	<5	NA
Normal weight	DAS28-remission						
	adalimumab	442	163	1 (ref.)	1 (ref.)	85	1 (ref.)
	etanercept	482	173	0.89 (0.61–1.31)	1.12 (0.71–1.77)	99	1.11 (0.80–1.54)
	infliximab	259	107	0.82 (0.53–1.28)	1.22 (0.71–2.11)	55	1.12 (0.76–1.65)
	abatacept	60	27	1.82 (0.82–4.08)	0.92 (0.34–2.49)	14	1.58 (0.80–2.98)
	DAS28-LDA						
	adalimumab	442	243	1 (ref.)	1 (ref.)	122	1 (ref.)
	etanercept	482	264	0.93 (0.64–1.37)	1.18 (0.74–1.88)	148	1.18 (0.89–1.58)
	infliximab	259	154	0.84 (0.54–1.30)	1.50 (0.86–2.62)	82	1.21 (0.86–1.69)
	abatacept	60	39	2.05 (0.87–4.84)	1.15 (0.39–3.35)	20	1.55 (0.85–2.76)
	RADAI-5-remission						
	adalimumab	442	109	1 (ref.)	1 (ref.)	49	1 (ref.)
	etanercept	482	125	1.15 (0.74–1.76)	1.08 (0.66–1.76)	69	1.37 (0.93–2.03)
	infliximab	259	71	1.11 (0.67–1.84)	1.16 (0.65–2.08)	38	1.40 (0.88–2.20)
	abatacept	60	17	1.36 (0.57–3.21)	1.79 (0.65–4.94)	9	1.62 (0.70–3.38)

ORadj for sex and age.
ORadj for sex, age, index year, baseline DAS28, csDMARD at index, steroid use at index.
*The median number of events among the imputed datasets.
CARRAC, confounder-adjusted response rate with attrition correction; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-remisison 28-joint, Disease Activity Score remission; LDA, low disease activity; MOIAN, Missing Outcome Information Assumed as No; n, number; NA, not applicable; ORadj, OR adjusted; RADAI-5-remission, Rheumatoid Arthritis Disease Activity Index-Five remission; ref, reference.

Table 3 Median change (delta, Δ) on individual clinical endpoints between baseline and the end of follow-up

	Adalimumab	Etanercept		Infliximab		Abatacept	
	Δ (IQR)	Δ (IQR)	P value	Δ (IQR)	P value	Δ (IQR)	P value
Obese							
ΔESR	−3.00(−11.50, 1.00)	−4.50 (−16.00, 1.00)	0.596	−0.50 (−5.00, 14.75)	0.044	−1.00 (−8.00, 2.00)	0.574
ΔCRP	−0.20 (−1.00, 0.00)	−0.45 (−0.94,−0.10)	0.389	0.35 (−0.24, 0.50)	0.047	−0.23 (−0.59, 0.00)	0.366
ΔTJC28	−3.00 (−6.00, 0.00)	−3.00 (−6.50,−0.50)	0.668	−1.00 (−6.00, 0.00)	0.642	−6.00 (−10.00,−0.75)	0.131
ΔSJC28	−2.00 (−7.00,−1.00)	−4.00 (−7.00,−0.50)	0.479	−2.00 (−5.50,−0.50)	0.648	−4.00 (−7.00,−2.00)	0.562
Overweight							
ΔESR	−4.00 (−12.00, 2.00)	−3.00 (−12.00, 2.00)	0.738	−3.50 (−15.25, 2.00)	0.989	−8.00 (−13.00,−5.00)	0.301
ΔCRP	−0.40 (−1.40, 0.00)	0.00 (−0.50, 0.00)	0.019	−0.28 (−0.73,−0.00)	0.452	−0.35 (−0.67, 0.00)	0.435
ΔTJC28	−3.00 (−6.75, 0.00)	−3.00 (−8.00, 0.00)	0.713	−3.00 (−7.50, 0.00)	0.882	−3.50 (−8.75,−1.00)	0.627
ΔSJC28	−3.00 (−7.00,−1.00)	−3.00 (−7.00, 0.00)	0.613	−4.00 (−8.50,−1.00)	0.306	−3.00 (−5.50,−0.50)	0.631
Normal weight							
ΔESR	−3.00 (−14.00, 1.00)	−4.00 (−13.00, 1.00)	0.942	−8.00 (−18.00, 0.00)	0.040	−8.00 (−17.00, 0.00)	0.290
ΔCRP	−0.15 (−0.60, 0.00)	−0.10 (−0.90, 0.00)	0.808	−0.41 (−1.45, 0.00)	0.173	−0.10 (−0.64, 0.00)	0.701
ΔTJC28	−3.00 (−7.00, 0.00)	−2.00 (−6.00, 0.00)	0.208	−3.00 (−8.50, 0.00)	0.217	−4.00 (−8.00,−2.00)	0.158

Significance tests compare each drug of interest to adalimumab, using Kruskal-Wallis test.
CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; SJC28, Swollen Joint Counts counting 28; TJC28, Tender Joint Counts counting 28.

The change in individual parameters is presented in table 3. We found no significant differences between abatacept and adalimumab in the improvement of individual parameters, independently of the BMI category. Conversely, compared with adalimumab, obese infliximab users had significantly worse improvement (less reduction) on ESR and CRP within the first year following treatment initiation. No differences in the change of individual parameters were identified in the overweight cohort between adalimumab and infliximab. However, in the normal weight cohort, patients with infliximab had better improvement on ESR and SJCs compared with adalimumab users.

Kaplan-Meier curves are depicted in online supplemental figure S4. No differences in drug survival were identified across the study drugs. Kaplan-Meier curves stratified by reason of treatment stop (adverse event(s); remission) as recorded by the clinician are shown in online supplemental figure S5.

DISCUSSION

This observational cohort study in the SCQM registry included 443 obese, 829 overweight and 1243 normal weight patients with RA treated with adalimumab, etanercept, infliximab or abatacept as their first b/tsDMARD. Similar achievement of DAS28-remission and DAS28-LDA were observed between the studied biologics compared with adalimumab, independently of the BMI cohort.

Our findings were in agreement with published studies in general RA populations.[4 30–32] For example, a recent observational cohort study of patients with RA who were new users of b/tsDMARDs showed no statistical differences in effectiveness between TNF inhibitors and non-TNF biologics,[30] and a study on new users of adalimumab, etanercept, infliximab and abatacept reported comparable rates of effectiveness across the study drugs (24%, 28%, 23%, 26%, respectively).[33]

Previous evidence suggested abatacept as a preferable drug candidate to treat patients with elevated BMI due to an alternative mode of action. This is supported by the systematic review from Shan and Zhang, which reported reduced odds of response in patients with RA with obesity treated with TNF inhibitors but not in patients treated with abatacept.[14] Additionally, four studies have assessed the impact of BMI on the treatment response in patients with RA treated with abatacept, all suggesting that BMI does not impact the clinical response to abatacept in RA.[21–24] In addition to this, the pharmacokinetics of abatacept were consistently described regardless of BMI,[21] despite abatacept being a lipophilic drug.[22] This may suggest that the lower response reported in obese patients treated with TNF inhibitors may relate to the mechanistic pathway of these treatments and not solely to their body distribution. For example, body weight was described as a predictor of the formation of ADAbs in patients with RA treated with infliximab, potentially explained by the higher TNF-infliximab complexes due to the additional TNF consequence of the adipose tissue.[19] Therefore, non-TNF biologics open up as potential optimal treatments in obese patients with RA. However, while this seemed promising, we did not observe any direct benefit of being treated with abatacept versus adalimumab in any of the study cohorts. This is in agreement with the observed comparable efficacy between abatacept and adalimumab

in a head-to-head randomised trial.[34] Therefore, we trust that current evidence does not justify a superiority of abatacept versus adalimumab in patients with RA with obesity.

Strengths and limitations

The number of head-to-head trials in RA is increasing,[31] and while studies on the comparative effectiveness of b/tsDMARDs in real-world setting are rising, they remain limited. To our knowledge, this is the first real-world comparative effectiveness observational cohort study on biologics in patients with RA stratified by BMI category.

Recent EULAR recommendations suggest to consider multiple imputation techniques and/or causal inference models to address attrition due to treatment discontinuation prior outcome assessment.[27] Thus, we implemented the imputation model CARRAC, while still providing traditional approaches alongside it.

However, there are limitations to the current study. First, we were limited by sample size. Thus, although we intended to provide secondary stratification of the BMI cohorts by sex, these were excluded due to low statistical power. However, we acknowledge that due to the evidence on sexual dimorphism in body fat distribution and adipose function,[35–37] sex-disaggregated evidence on treatment response by BMI group remains of interest. We also acknowledge that one of the burdens contributing to the current limited sex-disaggregated health evidence is the associated restriction on sample size. Thus, while these data were not here presented to avoid conclusions on underpower analyses, we encourage researchers conducting meta-analyses of sex-disaggregated data in RA to contact us for information. Additionally, although underweight patients were a population of interest, sample size-wise was not feasible to address the research question in these patients. Another limitation was that we restricted our analysis to only four biologics. This decision was driven by the limited sample size for other b/tsDMARDs due to different times of approval in Switzerland and, importantly, due to former guidelines suggesting TNF inhibitors as preferable first b/tsDMARD choice until 2013.[38 39] While a prevalent-user design would have enabled us to investigate more treatments, we discarded this option to avoid confounding by indication, for example, driven by the expected different response to second-line treatments based on the type of response to the first b/tsDMARD (ie, primary vs secondary non-response[40]). We acknowledge the differences in the mean year of index date between the biologics, as well as its potential (unmeasured) impact on the results. However, restricting the study time would have substantially reduce the sample size. Finally, our analysis included a high number of comparisons (eg, comparative effectiveness analysis within three BMI strata and three primary or secondary outcomes). As a result, although the study showed reduced odds of achieving RADAI-5-remission among etanercept overweight users in comparison to the respective adalimumab group, this effect was not observed for the DAS28 outcomes, and a rationale to explain it is lacking, therefore, we acknowledge that this could be a chance finding.

CONCLUSIONS

Patients treated with etanercept, infliximab or abatacept had similar odds of achieving DAS28-remission or DAS28-LDA compared with those treated with adalimumab, irrespective of the BMI category. Therefore, our study did not confirm the suggested benefit of abatacept versus TNF inhibitors in patients with RA with obesity.

Preprint

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Contributors EV-Y, TB and AMB contributed to the study conceptualisation, design and methodology. Clinicians and patients of the SCQM Programme contributed to the data collection. AF, EV-Y and AMB contributed to the data acquisition from the data holder SCQM. EV-Y performed data curation, formal analysis, visualisation and investigation; EV-Y wrote the original draft manuscript. EV-Y, TB, AF and AMB contributed to the interpretations of the findings, provided input and read and approved the final manuscript. EV-Y acts as the guarantor.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study was reviewed by the ethics commission of the Canton of Zurich (KEK: Req-2020-00045). Pseudonymised data, without access to the code key, was provided by the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) registry to the researchers. Therefore, the commission waived the need for a full ethics authorisation.

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Data availability statement Data may be obtained from a third party and are not publicly available. Restrictions apply to the availability of these data. Data were obtained from the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) and its availability requires received approval and permission from the license holder (SCQM).

terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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