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Item Type	Journal Article
Authors	Baker, Joshua F;Reed, George W;Poudel, Dilli Ram;Harrold, Leslie R;Kremer, Joel M
Citation	Baker JF, Reed G, Poudel DR, Harrold LR, Kremer JM. Obesity and Response to Advanced Therapies in Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2022 Nov;74(11):1909-1916. doi: 10.1002/acr.24867. Epub 2022 Jul 27. PMID: 35143117.
DOI	10.1002/acr.24867
Journal	Arthritis care & research
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Download date	2025-05-21 05:17:32
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Link to Item	https://hdl.handle.net/20.500.14038/53193

Obesity and Response to Advanced Therapies in Rheumatoid Arthritis

Joshua F. Baker,¹  George Reed,² Dilli Ram Poudel,³ Leslie R. Harrold,⁴ and Joel M. Kremer⁵

Objective. We performed a study of tumor necrosis factor inhibitors (TNFi) compared to non-TNFi biologic therapies in rheumatoid arthritis to test whether body mass index (BMI) modified the effect of each therapy.

Methods. We utilized data from CorEvitas. We studied 3 clinical outcomes based on the Clinical Disease Activity Index (CDAI) at 6 months from therapy initiation: 1) achievement of low disease activity (LDA); 2) a change as large as the minimum clinically important difference (MCID); and 3) the absolute change. We categorized BMI and utilized restricted cubic splines to consider nonlinear associations. We used linear and logistic regression to evaluate associations with response, adjusting for confounders. To determine if comparative effectiveness of therapy varied by BMI, we tested for interactions between BMI and class of therapy.

Results. The sample included 2,891 TNFi and 3,010 non-TNFi initiators. Among all initiators, those with severe obesity experienced lower odds of achieving LDA or MCID and less improvement in CDAI score, although associations were attenuated with adjustment. Low BMI was associated with reduced response rates in adjusted models including lower odds of LDA (odds ratio 0.32 [95% confidence interval (95% CI) 0.15, 0.71], $P = 0.005$). Analyses stratified by TNFi and non-TNFi therapies demonstrated no differences in clinical response rates for TNFi versus non-TNFi across BMI categories (all P for interaction >0.05). Estimates for non-TNFi biologics fit within the 95% CI for TNFi.

Conclusion. This study observed lower response rates among obese and underweight patients and no evidence of a superior effect of non-TNFi therapy over TNFi therapy in particular BMI categories.

INTRODUCTION

There has been increasing interest in the precision use of biologic therapies in rheumatoid arthritis (RA), as the trial-and-error approach results in delays in achieving adequate disease control for many patients. Few patient characteristics have been defined to help inform the appropriate choice of initial therapy for the disease.

A number of studies have evaluated whether obesity, one of the most common comorbid conditions in patients with arthritis, might influence the response to biologic therapies for RA as summarized in recent reviews, pooled analyses, and meta-analyses (1–5). These studies have suggested lower rates of clinical response among obese patients with RA (6,7), although they also

demonstrate a high rate of heterogeneity and some evidence of publication bias (1). The evidence to date has, therefore, not allowed the rheumatology community to reach a consensus regarding whether obesity is associated with a refractory disease phenotype nor how the presence of obesity should modify the choice of RA therapy.

While obesity can influence symptoms of the disease through an association with osteoarthritis, centralized pain, and other comorbid conditions (8–10), it remains unclear whether poor response to therapy in obese patients might also be related to an influence on inflammatory or immune pathways. In addition, an important limitation of prior research is the absence of studies directly comparing the efficacy of RA therapies in the context of obesity. If obesity is associated with poor response to all

The opinions or assertions presented herein are the private views and opinions of the authors and do not represent the views of the Department of Veterans Affairs.

Supported by the Corrona Research Foundation. Dr. Baker's work was supported by the Department of Veterans Affairs (Clinical Science Research and Development Merit award [grant I01 CX001703] and Rehabilitation Research and Development Merit award [grant I01 RX003644]).

¹Joshua F. Baker, MD, MSCE: Philadelphia VA Medical Center and University of Pennsylvania, Philadelphia; ²George Reed, PhD: Corrona Research Foundation, Albany, New York; ³Dilli Ram Poudel, MD: Indiana Regional Medical Center, Indiana, Pennsylvania; ⁴Leslie R. Harrold, MD, MPH: Corrona Research

Foundation, Albany, New York, and University of Massachusetts Medical School, Worcester; ⁵Joel M. Kremer, MD: Corrona Research Foundation and Albany Medical College and the Center for Rheumatology, Albany, New York.

Author disclosures are available at <https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr.24867&file=acr24867-sup-0001-Disclosureform.pdf>.

Address correspondence to Joshua F. Baker, MD, MSCE, 5th Floor White Building, 3600 Spruce Street, Philadelphia, PA 19104. Email: bakerjo@uphs.upenn.edu.

Submitted for publication November 11, 2021; accepted in revised form February 8, 2022.

SIGNIFICANCE & INNOVATIONS

- Obesity and underweight are each associated with lower clinical response rates at 6 months among patients initiating advanced therapies for rheumatoid arthritis.
- This is the first study to compare the efficacy of tumor necrosis factor inhibitors (TNFi) to non-TNFi therapies among obese patients.
- The efficacy of TNFi and non-TNFi therapies was statistically similar among patients across the range of body mass.
- These findings suggest that obesity should not influence the choice of therapy between these options.

therapies, then it cannot inform treatment decisions. A head-to-head comparison of RA treatments by weight status, to date not performed to our knowledge, would provide the critical information to guide decisions in clinical practice.

To address this gap in the knowledge, and determine whether weight and obesity might be used to inform treatment decisions, we performed a head-to-head study using long-term observational data from the CorEvitas US observational registry comparing standardized outcomes in patients initiating tumor necrosis factor inhibitors (TNFi) compared with non-TNFi biologic therapies and directly tested whether obesity modified the effect of therapy.

MATERIALS AND METHODS

We utilized data from the CorEvitas (formerly Corrona) database. This registry was initiated in 2001 and is the largest independent database in North America collecting standardized outcome metrics from both rheumatologists and patients at intervals of every 3–6 months. We included all participants enrolled through April 30, 2021. Data are collected using structured case report forms that include medication use and dose, height, weight, RA clinical disease activity, function, comorbid illnesses, and adverse events (11). We included participants with a diagnosis of RA initiating either TNFi or non-TNFi biologic therapies as second- or third-line therapy (to reduce bias due to use of TNFi preferentially as first-line biologics). Patients in low disease activity (LDA) at therapy initiation or who did not have a 6-month follow-up visit were excluded. A flow chart for study inclusion is shown in Supplementary Figure 1, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24867>, and characteristics of those missing key data are shown in Supplementary Table 1, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24867>.

This study was carried out in accordance with the Declaration of Helsinki, and all patients were required to provide written

informed consent and authorization prior to participating. All participating investigators were required to obtain full Institutional Review Board (IRB) approval for conducting noninterventional research involving human subjects. Sponsor approval and continuing review was obtained through a central IRB (the New England Independent Review Board, NEIRB number 120160610). For academic investigative sites that did not receive a waiver to use the central IRB, full approval was obtained from the respective governing IRBs, and documentation was submitted to CorEvitas prior to initiating any study procedures. Patients were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Definitions of obesity. We evaluated the effect of body mass index (BMI) and obesity in 3 ways. We used World Health Organization guidelines to categorize BMI as underweight (<18.5 kg/m²), normal weight (≥18.5–24.9 kg/m²), overweight (≥25–29.9 kg/m²), obese (≥30–34.9 kg/m²), and severely obese (≥35 kg/m²). We also dichotomized the exposure and compared obesity (BMI >30 kg/m²) to normal and overweight (BMI 20–30 kg/m²). Finally, we explored BMI as a continuous variable, utilizing restricted cubic splines to consider nonlinear associations with the outcomes of interest.

Response outcomes. We studied 3 disease activity outcomes based on the Clinical Disease Activity Index (CDAI) at 6 months. These included the achievement of LDA (CDAI score <10), the achievement of a change at least as large as the minimum clinically important difference (MCID) (12), and the absolute change in CDAI score from baseline. The MCID cut points for improvement have been previously described as 12 for patients starting with a high CDAI score, 6 for those with a moderate CDAI score, and 1 for those with a low CDAI score.

For the binary outcomes, we imputed nonresponse if the initiator switched therapy prior to 6 months. For the change in CDAI score we used last observed CDAI score prior to switching. If the initiator discontinued therapy but did not start another biologic therapy by 6 months, we used the actual response at 6 months.

Covariable assessments. A number of covariables were collected at each registry visit. We evaluated factors prehypothetized to represent important predictors of response to therapy and included age, sex, race, comorbidities, smoking, CDAI score, use of other RA therapies including prednisone, prior biologic disease-modifying antirheumatic drug (bDMARD) therapies, and disease duration.

Statistical analysis. We used descriptive statistics to evaluate differences in covariates across BMI categories and between TNFi and non-TNFi initiators in order to inform adjusted models. We used mixed-effects logistic regression to evaluate the odds of achievement of LDA and MCID for CDAI score within the

6 months after starting therapy across BMI categories in the overall sample. Models were adjusted for a number of potential confounders, including baseline CDAI score, sex, age, disease duration, number of prior bDMARDs, prednisone use, smoking status, history of diabetes mellitus, hypertension, depression, and clustering by site. Mixed-effects models were estimated that accounted for potential correlation of initiations within site and potential differences across site in efficacy. A random effect of each site was estimated and adjusted for in the analyses. We also used mixed-effects linear regression to evaluate the absolute change in CDAI score across BMI categories, adjusting for confounders and clustering by site. To determine if the effect of therapy varied by BMI, we tested for interactions between BMI category and class of therapy (TNFi versus non-TNFi biologics) in the above models.

To characterize the association between obesity and clinical response more comprehensively, we used restricted cubic splines to evaluate BMI as a continuous variable while considering

the nonlinear association between BMI and clinical outcomes. Linear splines approximated the cubic spline fit in order to provide an approximate effect of BMI (per 1 kg/m²) above and below the estimated BMI for peak efficacy from the cubic spline (13). This allowed the analysis to better characterize nonlinear associations between BMI and clinical response. We used these models to provide adjusted predicted probabilities of LDA, MCID, and the absolute change in CDAI score within patients taking TNFi and those not taking TNFi and illustrated these predicted probabilities and the resulting confidence intervals.

In order to assess whether obesity might have influenced response to therapy through differences in drug distribution, we performed a sensitivity analysis evaluating associations between BMI and clinical response among both weight-based (administered on a mg/kg basis or dosed based on a weight threshold) versus fixed-dose therapies. To evaluate the impact of potential outliers, we also assessed associations between BMI and clinical response after excluding patients with

Table 1. Baseline patient characteristics by body mass index (BMI) category*

	Underweight (n = 57)	Normal weight (n = 1,408)	Overweight (n = 1,724)	Obese I (n = 1,299)	Severely obese II (n = 1,413)	P
Age, years	63.6 ± 16.0	58.6 ± 15.3	59.2 ± 12.2	58.4 ± 11.9	55.9 ± 11.3	<0.001
Male, no. (%)	5 (8.8)	208 (14.8)	418 (24.2)	312 (24.1)	197 (14.0)	<0.001
White, no. (%)	53 (91.2)	1,265 (91.5)	1,537 (90.2)	1,144 (89.8)	1,228 (88.1)	<0.001
Black, no. (%)	4 (7.0)	38 (2.7)	94 (5.5)	82 (6.4)	127 (9.1)	
BMI	16.8 ± 1.1	22.4 ± 1.8	27.5 ± 1.4	32.3 ± 1.4	41.2 ± 5.6	<0.001
Smoking, no. (%)						
Never	20 (36.4)	704 (50.4)	777 (45.4)	635 (50.7)	697 (49.6)	<0.001
Previous	14 (22.5)	408 (29.2)	671 (35.5)	447 (30.6)	551 (35.7)	
Current	21 (38.2)	286 (20.5)	358 (19.2)	265 (18.7)	232 (14.7)	
Duration RA	17.4 ± 13.4	12.8 ± 10.9	11.6 ± 10.1	11.0 ± 9.4	9.5 ± 8.3	<0.001
CDAI score	25.8 ± 11.7	25.6 ± 12.5	25.5 ± 12.2	25.5 ± 12.1	25.5 ± 11.9	0.99
Tender joint count in 28 joints	9.2 ± 6.5	9.0 ± 7.0	9.0 ± 7.0	9.1 ± 7.2	9.3 ± 7.1	0.69
Swollen joint count in 28 joints	7.0 ± 5.7	7.3 ± 5.7	7.1 ± 5.6	6.9 ± 5.7	6.4 ± 5.5	0.001
PtGA score	54.2 ± 27.1	49.6 ± 25.0	51.7 ± 24.3	55.4 ± 23.2	57.7 ± 23.1	<0.001
PhGA score	41.7 ± 23.0	42.7 ± 20.8	42.1 ± 20.9	40.0 ± 20.4	39.9 ± 20.6	<0.001
Patient assessment of pain	57.4 ± 24.9	52.7 ± 26.0	54.1 ± 25.4	57.8 ± 25.5	60.0 ± 24.0	<0.001
M-HAQ score	0.80 ± 0.69	0.61 ± 0.53	0.61 ± 0.51	0.67 ± 0.51	0.75 ± 0.52	<0.001
Diabetes mellitus, no. (%)	2 (3.5)	55 (3.9)	139 (8.1)	169 (13.0)	269 (19.0)	<0.001
CVD, no. (%)	9 (15.8)	156 (11.1)	211 (12.2)	188 (14.0)	188 (13.3)	0.16
Cancer, no. (%)	4 (7.0)	109 (7.7)	132 (7.7)	82 (6.3)	107 (7.6)	0.61
Hypertension, no. (%)	10 (17.5)	330 (23.4)	480 (27.8)	496 (38.2)	595 (42.1)	<0.001
Depression, no. (%)	9 (15.8)	306 (21.7)	404 (23.4)	305 (23.5)	424 (30.0)	<0.001
TNFi (vs. non-TNFi), no. (%)	26 (46)	653 (46)	865 (50)	629 (48)	718 (51)	0.13
Prednisone, no. (%)	24 (42.1)	517 (36.7)	557 (32.3)	422 (32.5)	421 (29.8)	0.001
Methotrexate, no. (%)	22 (38.6)	708 (50.3)	886 (51.4)	682 (52.5)	767 (54.3)	0.06
csDMARD, no. (%)	35 (61.4)	965 (68.5)	1,193 (69.2)	924 (71.1)	1,043 (73.8)	0.008
Line of therapy, no. (%)						
2nd line	33 (57.9)	856 (60.8)	1,047 (59.8)	777 (59.8)	833 (59.0)	0.82
3rd line	24 (42.1)	552 (39.3)	522 (39.3)	580 (40.2)	580 (41.0)	

* Values are the mean ± SD unless indicated otherwise. CDAI = Clinical Disease Activity Index; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CVD = cardiovascular disease; M-HAQ = modified Health Assessment Questionnaire; PhGA = physician global assessment of disease activity; PtGA = patient global assessment of disease activity; RA = rheumatoid arthritis; TNFi = tumor necrosis factor inhibitor.

Table 2. Characteristics of patients initiating tumor necrosis factor inhibitor (TNFi) and non-TNFi biologics*

	Non-TNFi (n = 3,010)	TNFi (n = 2,891)	P
Age, years	59.4 ± 12.7	56.31 ± 12.90	<0.001
Male, no. (%)	601 (20.0)	539 (18.7)	0.18
White, no. (%)	2,678 (90.4)	2,549 (89.5)	0.02
Black, no. (%)	161 (5.4)	184 (6.5)	
BMI, kg/m ²	30.4 ± 7.5	30.7 ± 7.7	0.03
Smoking, no. (%)			
Never	1,452 (48.6)	1,399 (48.7)	0.09
Previous	1,012 (33.9)	914 (31.8)	
Current	523 (17.5)	559 (19.5)	
RA duration, years	12.2 ± 10.3	10.4 ± 9.3	<0.001
CDAI score	26.1 ± 12.3	24.9 ± 12.0	<0.001
Tender joint count in 28 joints	9.3 ± 7.1	8.8 ± 7.0	0.02
Swollen joint count in 28 joints	7.2 ± 5.8	6.6 ± 5.5	<0.001
PtGA score	54.0 ± 23.8	52.9 ± 24.5	0.08
PhGA score	41.8 ± 20.7	41.6 ± 20.6	0.03
Patient assessment of pain	56.8 ± 25.1	55.5 ± 25.7	0.10
M-HAQ score	0.68 ± 0.53	0.63 ± 0.51	<0.001
Diabetes mellitus, no. (%)	323 (10.7)	311 (10.8)	0.97
CVD, no. (%)	421 (14.0)	325 (11.2)	0.002
Cancer, no. (%)	249 (8.3)	185 (6.4)	0.006
Hypertension, no. (%)	1,025 (34.1)	866 (30.6)	0.002
Depression, no. (%)	725 (24.1)	723 (25.0)	0.27
Prednisone, no. (%)	1,070 (35.5)	871 (30.1)	<0.001
Methotrexate, no. (%)	1,496 (49.7)	1,569 (54.3)	<0.001
csDMARD, no. (%)	2,174 (67.9)	2,398 (72.6)	<0.001
Line of therapy, no. (%)			
2nd line	1,469 (48.8)	2,077 (71.8)	<0.001
3rd line	1,541 (51.2)	814 (28.2)	

* Values are the mean ± SD unless indicated otherwise. BMI = body mass index; CDAI = Clinical Disease Activity Index; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CVD = cardiovascular disease; M-HAQ = modified Health Assessment Questionnaire; PhGA = physician global assessment of disease activity; PtGA = patient global assessment of disease activity; RA = rheumatoid arthritis.

very low BMI (<18.5 kg/m²). We also used inverse probability weighting to account for the potential effect of missing data in the analysis. This approach yielded highly similar results to the primary analysis (data not shown).

RESULTS

A total of 5,901 initiations in 5,050 unique patients were included in the current analysis. Of these, 2,712 were either obese or severely obese (46%) at time of initiation, with a mean ± SD BMI for the group of 30.5 ± 7.6. There were a number of patient characteristics that were different by BMI category including age, modified Health Assessment Questionnaire (M-HAQ) score, sex, race, smoking status, comorbidities, prednisone use, and conventional synthetic DMARD (csDMARD) use (Table 1). There were no differences in the number of prior bDMARDs.

The sample included 2,891 TNFi initiators and 3,010 non-TNFi initiators. Initiators of non-TNFi therapies were older, had longer disease duration, higher CDAI score, higher M-HAQ score, were more likely to use prednisone, less likely to use csDMARDs, more likely to be initiating third-line biologic therapy, and more likely to have comorbidities including cardiovascular disease, cancer, and hypertension compared to initiators of TNFi (Table 2).

There was a similar rate of drug discontinuation and switching across BMI categories over 6 months of follow-up among both TNFi and non-TNFi initiators ($P = 0.682$; see Supplementary Table 2, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24867>).

In analyses including all biologic initiators, initiators with severe obesity experienced significantly lower odds of achieving LDA or MCID response and less improvement in the CDAI score (Table 3). In adjusted models, these associations were no longer statistically significant. For example, severe obesity was associated with numerically lower odds of LDA, although the confidence interval crossed 1 in adjusted models (odds ratio [OR] 0.88 [95% confidence interval (95% CI) 0.74, 1.06], $P = 0.18$).

In adjusted models, low BMI (compared to normal BMI) was associated with significantly lower odds of achievement of LDA (OR 0.32 [95% CI 0.15, 0.71], $P = 0.005$) and MCID (OR 0.40 [95% CI 0.21, 0.75], $P = 0.005$) and more modest improvements in CDAI score (β 4.33 [95% CI 1.26, 7.40], $P = 0.006$). The latter coefficient suggests a 4-point lesser improvement among those with low BMI compared to normal weight.

Analyses stratified by TNFi and non-TNFi therapies demonstrated similar observations, with no significant differences in the

Table 3. Disease response by body mass index (BMI) category in the overall sample for unadjusted and adjusted models*

	CDAI LDA unadjusted, OR (95% CI)	CDAI LDA adjusted, OR (95% CI)†	CDAI MCID unadjusted, OR (95% CI)	CDAI MCID adjusted, OR (95% CI)†	ΔCDAI unadjusted, β (95% CI)	ΔCDAI adjusted, β (95% CI)†
BMI category						
Underweight	0.34 (0.16, 0.2)	0.32 (0.15, 0.71)	0.44 (0.24, 0.81)	0.40 (0.21, 0.75)	3.98 (0.34, 7.63)	4.33 (1.26, 7.40)
Normal	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	0 (ref.)	0 (ref.)
Overweight	1.11 (0.95, 1.29)	1.08 (0.92, 1.27)	1.01 (0.88, 1.17)	0.98 (0.84, 1.14)	-0.24 (-1.21, 0.73)	-0.26 (-1.7, 0.55)
Obese	1.02 (0.87, 1.20)	1.01 (0.85, 1.21)	1.04 (0.89, 1.21)	1.03 (0.88, 1.22)	0.25 (-0.79, 1.28)	0.24 (-0.64, 1.12)
Severely obese	0.80 (0.68, 0.94)	0.88 (0.74, 1.06)	0.81 (0.70, 0.94)	0.89 (0.75, 1.05)	0.97 (-0.04, 1.98)	0.30 (-0.59, 1.18)
LR test P value	<0.001	0.004	<0.001	0.015	0.030	0.015
Obese (vs. non-obese)	0.76 (0.67, 0.87)	0.85 (0.74, 0.99)	0.81 (0.72, 0.91)	0.88 (0.77, 1.01)	0.99 (0.17, 1.82)	0.31 (-0.40, 1.02)

* 95% CI = 95% confidence interval; CDAI = Clinical Disease Activity Index; LDA = low disease activity; LR = likelihood ratio; MCID = minimum clinically important difference; OR = odds ratio; ref. = reference.

† Adjusted for baseline CDAI score, sex, age, disease duration, line of therapy, prednisone use, smoking status, history of diabetes mellitus, hypertension, depression, and clustering by site.

effect of TNFi or non-TNFi on clinical response across BMI categories (all P for interaction >0.05) (Table 4). For example, severe obesity was not associated with LDA among either TNFi (OR 0.96 [95% 0.74, 1.23]) or non-TNFi biologic therapies (OR 0.82 [95% CI 0.64, 1.05]), with no difference in the association between obesity and clinical response across the 2 therapies (P for interaction = 0.68). Similar patterns of association were observed for MCID (Table 4) and for the absolute change in CDAI score at 6 months (see Supplementary Table 3, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24867>), with no evidence of statistical interaction.

In models incorporating restricted cubic splines, the best response rates were observed among patients with a BMI near 27 kg/m² (see Supplementary Figure 2 available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24867>). Quantitative trends were approximated

using linear splines (see Supplementary Figure 3 available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24867>). There was a decrease in the likelihood of achievement of LDA and MCID as BMI decreased below 27 kg/m² (OR for LDA [per 1 kg/m²] 0.959 [95% CI 0.931, 0.987]; OR for MCID [per 1 kg/m²] 0.969 [95% CI 0.943, 0.996]). As BMI increased above 27 kg/m², the odds of achievement of LDA and MCID also decreased (OR for LDA [per 1 kg/m²] 0.979 [95% CI 0.968, 0.990]); OR for MCID [per 1 kg/m²] 0.988 [95% CI 0.978, 0.998]). The absolute change in CDAI score also fits a similar pattern, with less of a reduction in CDAI score for each 1 kg/m² below a BMI of 27 kg/m² (β 0.159 [95% CI 0.019, 0.300]) and less of a reduction in CDAI score for each 1 kg/m² >27 kg/m² (β 0.070 [95% CI 0.016, 0.124]). In these analyses using restricted cubic splines, there were no significant interactions in the effect of BMI by TNFi or non-TNFi therapies. Figure 1 demonstrates that the estimates for non-TNFi biologics fit within the 95% CI for TNFi

Table 4. Achievement of Clinical Disease Activity Index (CDAI) low disease activity (LDA) and minimum clinically important difference (MCID) (adjusted) by 6 months by body mass index (BMI) category and stratified by tumor necrosis factor inhibitor (TNFi) and non-TNFi therapies (estimates derived from single regression model with interaction term)*

BMI category	LDA		P interaction†	MCID		P interaction†
	TNFi OR (95% CI)	Non-TNFi OR (95% CI)		TNFi OR (95% CI)	Non-TNFi OR (95% CI)	
Underweight	0.28 (0.08, 1.01)	0.35 (0.13, 0.97)	0.678	0.22 (0.07, 0.70)	0.56 (0.25, 1.23)	0.266
Normal	1 (ref.)	1 (ref.)		1 (ref.)	1 (ref.)	
Overweight	1.10 (0.87, 1.40)	1.07 (0.85, 1.33)		0.99 (0.80, 1.24)	0.98 (0.79, 1.21)	
Obese	1.14 (0.88, 1.47)	0.91 (0.71, 1.16)		1.09 (0.87, 1.36)	0.92 (0.74, 1.12)	
Severely obese	0.96 (0.74, 1.23)	0.82 (0.64, 1.05)		0.86 (0.69, 1.07)	0.90 (0.71, 1.12)	
Obese vs. non-obese	0.88 (0.72, 1.08)	0.82 (0.67, 1.01)	0.613	0.85 (0.70, 1.02)	0.92 (0.76, 1.11)	0.524

* Adjusted for baseline CDAI score, sex, age, disease duration, line of therapy, prednisone use, smoking status, history of diabetes mellitus, hypertension, depression, and clustering by site. 95% CI = 95% confidence interval; OR = odds ratio; ref. = reference.

† Based on likelihood ratio test of models with and without interaction term.

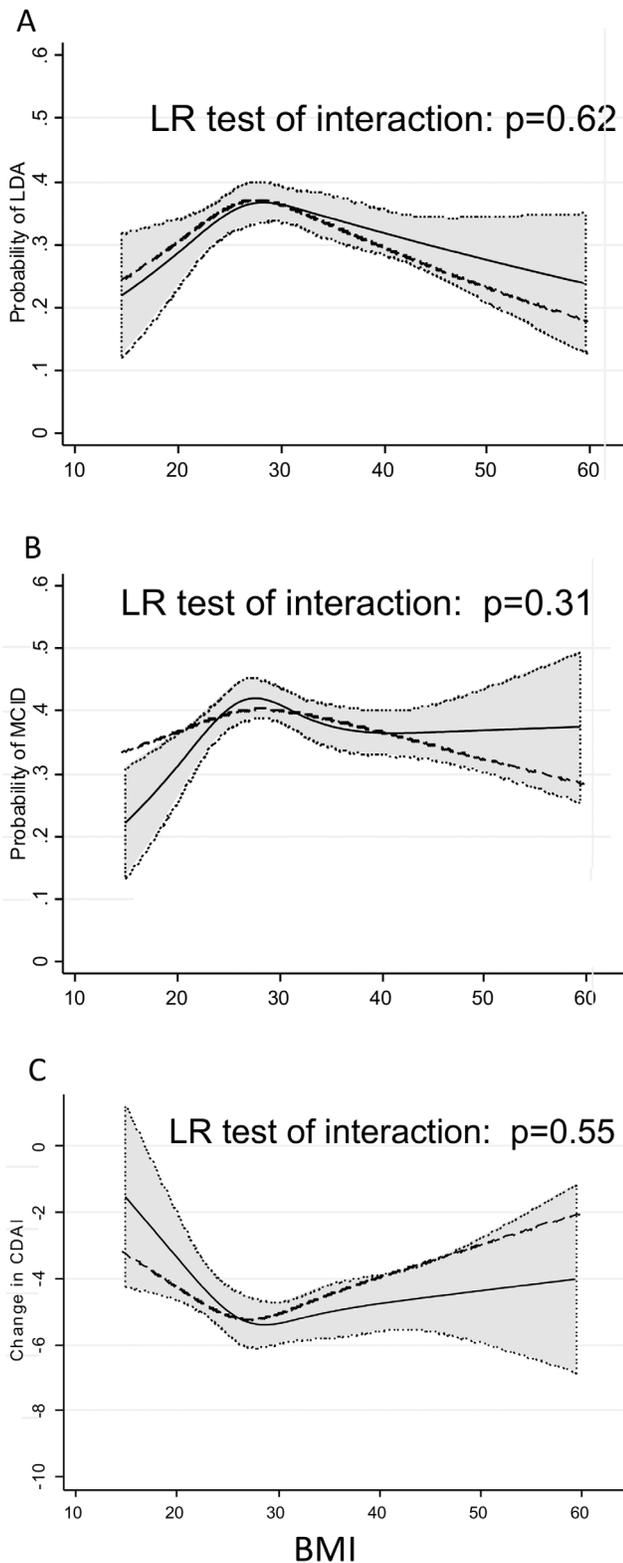


Figure 1. Linear splines with knot at 27 kg/m^2 demonstrating association between body mass index (BMI) and clinical response as defined by low disease activity (LDA) (A), minimum clinically important difference (MCID) (B), and absolute change in Clinical Disease Activity Index (CDAI) score (C) with stratification by tumor necrosis factor inhibitor (TNFi) (solid lines) and non-TNFi biologics (broken lines). The shaded area shows the 95% confidence interval. LR = likelihood ratio.

biologics for analyses evaluating LDA, MCID, and absolute changes in CDAI score, respectively.

The associations between BMI and clinical responses were similar among therapies with weight-based dosing and those without (see Supplementary Figure 4 available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24867>). The associations were also similar when excluding patients with a BMI of $<18.5 \text{ kg/m}^2$ (see Supplementary Figure 5 available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24867>).

DISCUSSION

We observed for the first time a similar reduction in response to therapy among both TNFi and non-TNFi therapies among patients with severe obesity. This is also among the first studies to describe significant lower response rates among underweight patients. The key advance over prior literature is the absence of a significant difference in the effect of TNFi versus non-TNFi biologics according to BMI in a well-powered comparative study. These head-to-head results are important because they suggest that the presence of obesity should not influence the choice of TNF versus non-TNF therapy.

One of the key findings from the current analysis that advances the literature is lack of effect modification for TNFi and non-TNFi therapies across BMI categories. A number of prior studies and meta-analyses have suggested poor response to TNFi among patients who are obese (6,7,14). While we are not aware of head-to-head comparative effectiveness studies in this area, 1 study by Schafer et al (15) compared the association between obesity and clinical response across RA therapies in a large observational cohort study (Rheumatoid Arthritis: Observation of Biologic Therapy [RABBIT]). Among 10,593 RA patients, followed for 5–10 years, they observed that, while the magnitude of association between obesity and clinical response was similar across all biologic therapies, a statistically significant association was only observed among patients taking TNFi and tocilizumab (15). Our current study suggests that a lack of response among obese patients is not specific to TNFi therapies, suggesting that this phenomenon is not biologically specific to the TNF pathway. As noted, the direct impact of these observations is to suggest that obesity should not inform the effectiveness of different classes of biologic therapies or factor into clinical decision-making.

This study used several outcomes to quantify overall clinical response to therapy across BMI categories. We have, for what we believe is the first time, also utilized restricted cubic splines to evaluate the nonlinear association between BMI and response to therapy in order to characterize these relationships more completely. We observed for the first time that optimal response rates might be expected within the overweight category of BMI ($25\text{--}30 \text{ kg/m}^2$). Patients with either lower or higher BMI can be expected to have a lower probability of response, although this

difference may only be clinically relevant in patients with either very low BMI (<18.5 kg/m²) or who are severely obese BMI (>35 kg/m²). Some of the association between obesity and clinical response was explained by other factors, and residual confounding may be present.

Obesity may affect clinical response rates through a variety of mechanisms, none of which can be clearly delineated here. Obesity is associated with a number of comorbidities (e.g., osteoarthritis, amplified pain) that may affect perceived response to therapy (e.g., inflation of patient global scores) (16,17). As noted, adjusting for comorbidities reduced the observed association between obesity and clinical response in our study, suggesting that confounding related to comorbid conditions likely plays a role. Because obesity has been associated with reduced rates of radiographic progression and lower synovitis and osteitis on imaging, and because it has no impact on the achievement of low inflammation on magnetic resonance imaging in a clinical trial setting (18,19), it seems unlikely that refractory inflammatory disease is the explanation. However, we are unable to rule out a potential link between obesity and more active and refractory inflammatory arthritis in this study.

Low BMI has been associated with poor outcomes in RA in other studies. For example, low BMI has been associated with greater inflammatory disease on imaging as well as a high rate of adverse long-term outcomes, such as radiographic progression and early mortality (18,20–22). We also previously showed that persistence of biologic and conventional therapies was lower among thin patients with RA (23). However, to our knowledge, our current finding of an association with response to therapy at 6 months from initiation of biologic therapy is novel. There is thus some evidence to suggest that patients with BMI below the normal range might have a more severe phenotype of disease, perhaps resulting in weight loss and sarcopenia over time. It is not the authors' hypothesis that a BMI below the normal range has adverse causal impact on the disease but rather that it is more likely to occur in association with aging, comorbidity, and the disease process itself. Thus, poor metabolic health is proposed to explain poor clinical response rates in this group. This relationship is not completely understood and deserves further study (18,24).

To create a more acceptable comparison between biologic therapies, we only included patients who were not naive to biologics. Thus, while there is no reason to suggest that these observations would not apply to biologics-naïve patients, this was not directly studied. While this is the largest study to address this question to our knowledge, it is not possible to rule out very small differences in the association between obesity and clinical response by therapy, although it is unlikely that smaller differences are clinically meaningful. Also, despite the large sample size, there were relatively few underweight patients in particular. Similarly, while our analyses did not suggest that treatments with weight-based dosing were less affected by obesity, we were unable to rule out small differences. An important limitation in studying obesity in this context is the difficulty differentiating mediators of the

relationship between obesity and disease activity and response to therapy. Further study focused on why obesity might affect clinical response would be of value. Finally, we did not explore off-label dosing strategies or dosing intervals, although our approach is consistent with the real-world use of these therapies. Strengths of the study include the large sample of well-characterized patients, robust consideration of confounding factors, consistency across multiple approaches and sensitivity analyses, and the direct comparison of RA therapies.

In conclusion, this study found evidence to support lower response rates among obese and underweight patients with RA, with no evidence of a superior effect of non-TNFi therapy over TNFi therapy in particular BMI categories. The immediate implication of these results is to suggest that, while lower response rates may be expected in underweight and severely obese patients with RA, weight and BMI should not influence the choice of biologic therapy at least in terms of clinical efficacy.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Baker had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Baker, Reed, Poudel, and Kremer.

Acquisition of data. Kremer.

Analysis and interpretation of data. Baker, Reed, Harrold, and Kremer.

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