

# The Effect of Adiposity on Anti-Tumor Necrosis Factor-Alpha Levels and Loss of Response in Crohn's Disease Patients

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**INTRODUCTION:** A high body mass index is known to adversely affect antitumor necrosis factor-alpha trough levels and secondary loss of response (SLOR) in patients with Crohn's disease. We hypothesize that high levels of adiposity negatively affect these outcomes and aimed to determine if this relationship exists.

**METHODS:** We performed a retrospective cross-sectional study of 69 patients with Crohn's disease from two tertiary inflammatory bowel disease centers between February 1, 2015, and June 30, 2018. Primary responders to infliximab (IFX) or adalimumab (ADA) who had a trough level performed within 6 months of CT or MRI scan and at least 12 months of clinical follow-up were eligible for inclusion. Body composition as measured on CT/MRI scans were correlated with trough concentration and time SLOR. Multivariate adjustments were made for established risk factors known to affect trough levels and SLOR.

**RESULTS:** Of 69 included patients, 44 (63.8%) and 25 (36.2%) patients received IFX and ADA, respectively. Multivariate analysis revealed that IFX trough concentrations were inversely correlated with visceral fat area ( $-0.02$  [ $-0.04$ ,  $-0.003$ ],  $P = 0.03$ ), visceral fat index ( $-0.07$  [ $-0.12$ ,  $-0.01$ ],  $P = 0.02$ ) and visceral fat: skeletal muscle area ratio ( $-3.81$  [ $-7.13$ ,  $-0.50$ ],  $P = 0.03$ ), but not body mass index ( $-0.23$  [ $-0.52$ ,  $0.06$ ],  $P = 0.11$ ). No predictive factors were found for ADA. Increased total adipose area was associated with an increased risk of SLOR in ADA-treated patients, but not IFX-treated patients (hazard ratio = 1.01 [1.002, 1.016],  $P = 0.011$ ).

**DISCUSSION:** Visceral adiposity is an important predictor of IFX trough levels, and high total adiposity predicts for SLOR to ADA.

**SUPPLEMENTARY MATERIAL** accompanies this paper at <http://links.lww.com/CTG/A374>; <http://links.lww.com/CTG/A375>

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## INTRODUCTION

Inflammatory bowel disease (IBD) and obesity are increasing in incidence and prevalence worldwide (1). Increased adiposity has been shown to worsen the clinical outcomes of IBD including increased frequency of disease flares, postoperative recurrence, and stricturing/penetrating complications (2–6). The antitumor necrosis factor-alpha (TNF $\alpha$ ) agents are effective in treating IBD but have a primary nonresponse rate of 10%–30% and secondary loss of response (SLOR) rate of 10%–15% per year (7), which may be attributed to several patient and disease- and treatment-related factors. One of these factors is a high body mass index (BMI). It is unknown, however, if it is simply a large total body mass or a large adipose mass in high BMI patients that result in lower anti-TNF $\alpha$

drug levels and loss of response. We hypothesize that visceral adiposity is inversely correlated with anti-TNF $\alpha$  drug levels and positively correlated with the risk of developing SLOR in patients with Crohn's disease (CD). Our aim was to investigate the impact of various body composition area measurements (total fat area [TFA], subcutaneous fat area [SFA], visceral fat area [VFA], skeletal muscle area [SMA], and abdominal circumference [AC]) as measured by cross-sectional imaging on anti-TNF $\alpha$  drug levels and SLOR.

## MATERIALS AND METHODS

### Study population

The study population comprised patients aged at least 16 years of age from 2 tertiary IBD centers in Western Australia. The

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prospectively maintained clinical databases of these 2 centers were interrogated and cross-referenced with hospital pharmacy dispensary records from January 1, 2015, to June 30, 2018. All included patients were primary responders to an anti-TNF $\alpha$  after at least 12 weeks of therapy and entered the study on standard dosing regimens of infliximab (IFX) or adalimumab (ADA) (i.e., 5 mg/kg 8-weekly or 40 mg every other week, respectively). Patients were included in the study cohort if they had CD, an anti-TNF $\alpha$  drug level taken within 6 months of a CT or MRI examination, and had at least 12 months of clinical follow-up data available (Figure 1). The clinical progress of each patient was followed until the censor date of June 30, 2019.

### Outcomes

The primary outcome was the anti-TNF $\alpha$  trough concentration (IFX or ADA) measured by a standard ELISA assay (PROMONITOR) in micrograms per milliliter, and the secondary outcome was the time to SLOR in months. The assay for measuring antibodies was a drug-sensitive assay. Antibody levels that were >100 AU/mL were considered neutralizing antibodies. Lower level antibodies were retested, and if they disappeared, they were not considered neutralizing antibodies. Antibody levels that

remained positive but at a titre <100 AU/mL with a detectable anti-TNF $\alpha$  trough level were not considered neutralizing and was clinically managed with anti-TNF $\alpha$  dose escalation and/or the addition of an immunomodulator, irrespective of whether the patients were experiencing symptoms of a flare.

### Definitions

SLOR was defined as an initial response to standard induction therapy (5 mg/kg IFX at week 0, 2, and 6 or 160/80 mg of ADA at week 0 and 2), followed by any increase in clinical disease activity score assessed by the Harvey-Bradshaw index, accompanied by either a raised inflammatory biomarker (C-reactive protein [CRP] and/or faecal calprotectin) and/or the endoscopic evidence of active disease, and the need for treatment escalation (anti-TNF $\alpha$  reinduction, dose escalation, a switch out of class,  $\geq$ 2 steroid courses per year, or the need for operative intervention).

### Variables

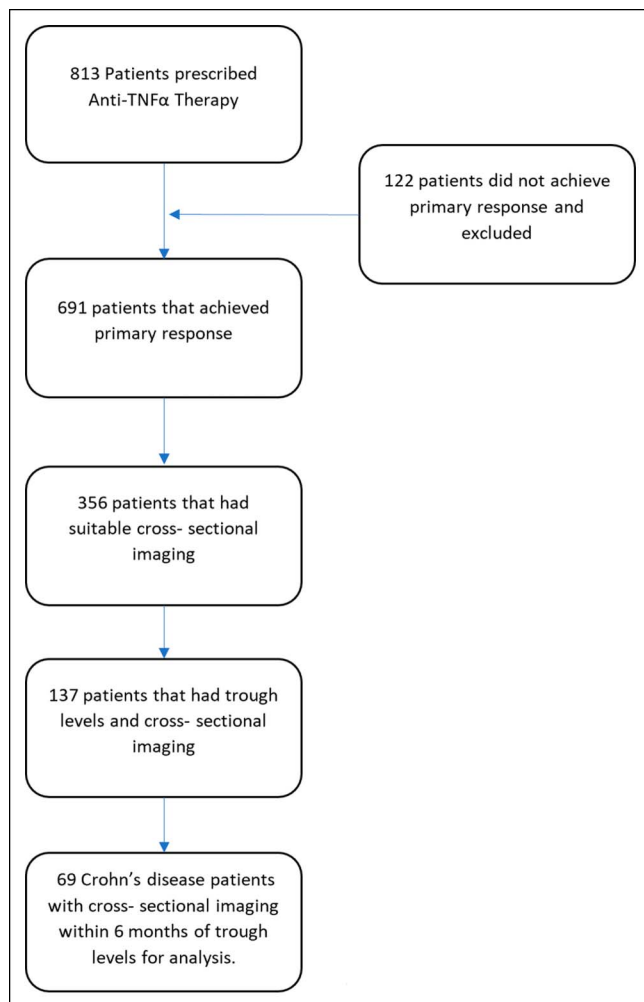
Patient-, disease-, and therapy-related variables evaluated are summarized in Table 1. Body weight in kilograms and height and meters within a month of the trough levels were obtained from infusion charts and outpatient notes. Complete blood counts, serum albumin, and CRP levels, taken within a month of the anti-TNF $\alpha$  levels, were obtained from electronic medical records. Body composition areas measured in squared centimeter through the L3 vertebral level on CT and MRIs TFA, VFA, SFA, and lumbar SMA as well as AC in centimeters.

### Radiological method to measure body compartment areas

A single radiologist (C.J.W.) blinded to the clinical data reviewed the CT/MRI scans and calculated the compartment areas of interest in squared centimeters. Study images were obtained using a range of multislice CT and 1.5 T MRI scanners from different manufacturers according to standard protocols for imaging CD. Subject images were retrieved in Digital Imaging and Communications in Medicine format. A single Digital Imaging and Communications in Medicine image was obtained at the L3 vertebral body level from each subject as previously described (8).

For CT, the 3-mm axial slice was cross-referenced with the sagittal reformatted images. For MRI, the axial slice was cross-referenced with the coronal half-fourier acquisition single-shot turbo spin echo or volumetric interpolated breath-hold examination sequences. The slice was obtained from the middle of the L3 vertebral body, unless there was significant artefact at that level, in which case the first slice immediately cranial or caudal to this level was chosen. Half-fourier acquisition single-shot turbo spin echo, true fast imaging with steady state precession and volumetric interpolated breath-hold examination images were assessed.

Owing to the retrospective nature and multimodality combination of CT and MRI images in this study and the absence of nonfat-saturated T1-weighted images in some patients (for which most available MRI segmentation software require), body composition was performed on all subjects using the National Institutes of Health ImageJ software (Version 1.52a) to ensure technique standardization. For CT images, the Hounsfield unit value ranges were used to differentiate between the fat and muscle components based on tissue-specific attenuation values for skeletal muscle (-29, +150) and adipose tissue (-190, -30) (8). For MRI images, visual identification of tissue planes was performed by the blinded radiologist to manually segment the images. A previous analysis of body composition assessments using



**Figure 1.** Flow diagram of patients who met the inclusion criteria. TNF $\alpha$ , tumor necrosis factor- $\alpha$ .

**Table 1.** Correlation of baseline clinical characteristics with trough levels of infliximab (IFX) and adalimumab (ADA)

Characteristics	Overall	IFX (n = 44)	ADA (n = 25)	Correlation (Rs) <sup>a</sup> with trough level: IFX patients (n = 44)	Correlation with trough level: ADA patients (n = 25)
Gender					
Male	42 (60.9)	28 (63.6)	14 (56.0)	-0.12	0.25
Female	27 (39.1)	16 (36.4)	11 (44.0)		
Age (yr)	43.5 ± 16.2	43.2 ± 16.2	44.0 ± 16.5	-0.13	0.02
Smoking status at the time of trough level					
Active smoking	16 (23.2)	8 (18.2)	8 (32.0)	0.31 <sup>b</sup>	-0.07
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 (1.6–1.8)	0.19	-0.29
Weight (kg)	79.0 ± 15.6	80.0 ± 16.7	79.6 (66.7–87.0)	-0.12	-0.31
BMI (kg/m <sup>2</sup> )	26.9 ± 5.1	27.2 ± 4.9	25.5 (21.5–30.2)	-0.26	-0.16
Any metabolic risk factor <sup>c</sup>	13 (18.8)	8 (18.2)	5 (20.0)	0.05	0.04
Any extraintestinal manifestations <sup>d</sup>	14 (20.3)	10 (22.7)	4 (16.0)	-0.11	0.03
Any inflammatory disease condition <sup>e</sup>	4 (5.8)	2 (4.5)	2 (8.0)	0.15	-0.47 <sup>b</sup>
Montreal: CD age at diagnosis					
≤16	11 (15.9)	8 (18.2)	3 (12.0)	0.07	-0.32
17–40	43 (62.3)	27 (61.4)	16 (64.0)		
>40	15 (21.7)	9 (20.5)	6 (24.0)		
Montreal: CD location					
L1	23 (33.3)	15 (34.1)	8 (32.0)	-0.03	0.03
L2	8 (11.6)	6 (13.6)	2 (8.0)		
L3	38 (55.1)	23 (52.3)	15 (60.0)		
L4	8 (11.6)	4 (9.1)	4 (16.0)	-0.19	0.21
Montreal: CD behavior					
B1	15 (21.7)	11 (25.0)	4 (1.0)	-0.13	-0.06
B2	36 (52.2)	21 (47.7)	15 (60.0)		
B3	18 (26.1)	12 (27.3)	6 (24.0)		
Montreal: CD perianal					
Harvey-Bradshaw index at the time of trough level	12.0 (10.0–15.0)	11.5 (9.8–15.0)	12.0 (10.0–15.0)	0.07	-0.03
Duration of therapy from induction to trough level (mo)	9.2 (3.3–27.0)	11.7 (5.0–29.1)	8.8 (2.9–23.6)	—	—
Duration of disease at trough level (mo)	94.0 (28.5–225.5)	105.5 (21.0–200.8)	94.0 (37.5–259)	—	—
Previous surgeries					
Any surgery	36 (52.2)	22 (50.0)	14 (56.0)	-0.19	0.14
No. of previous surgeries	1 (1–2)	1 (1–2)	1 (1–2)	-0.11	-0.01
Concurrent immunomodulator					
Yes	32.0 (46.4)	22.0 (50.0)	10.0 (40.0)	-0.02	0.24
Duration (mo)	25 (19–48)	25 (14–42)	29 (21–52)	-0.23	0.25
Corticosteroid use within 6 mo of imaging					
Yes	13.0 (18.8)	9.0 (20.5)	4.0 (16.0)	0.06	-0.03
Max dose of steroid	40.0 (30.0–50.0)	40.0 (40.0–40.0)	40.0 (30.0–50.0)	0.36	0.00
Secondary loss of response, <sup>f</sup> yes	36 (52.2)	24 (54.5)	12 (48.0)	-0.55 <sup>b</sup>	-0.33
Months to loss of response from induction	20.2 (13.8–35.6)	18.7 (12.6–35.6)	23.9 (15.3–36.6)	0.31 <sup>b</sup>	-0.09

Table 1. (continued)

Characteristics	Overall	IFX (n = 44)	ADA (n = 25)	Correlation ( <i>R</i> s) <sup>a</sup> with trough level: IFX patients (n = 44)	Correlation with trough level: ADA patients (n = 25)
Median trough level of anti-TNF $\alpha$ agent	5.5 (1.9–9.2)	4.9 (1.6–8.9)	6.1 (3.1–10.8)	—	—
Months between imaging and trough level	2.1 (0.9–3.4)	2.7 (0.8–4.7)	1.9 (0.9–2.5)	—	—
Months from imaging to loss of response	11.9 (3.0–18.8)	8.8 (2.4–19.4)	13.2 (7.4–17.8)	—	—
Hemoglobin <sup>b</sup>	139.9 $\pm$ 14.2	140.4 $\pm$ 14.4	138.9 $\pm$ 14.0	0.16	–0.54 <sup>b</sup>
Platelets <sup>b</sup>	275.3 $\pm$ 81.8	281.8 $\pm$ 83.3	263.8 $\pm$ 79.3	–0.28	0.18
CRP <sup>b</sup>	4.8 (1.3–11.0)	4.8 (1.7–13.8)	5.0 (1.0–9.5)	–0.38 <sup>b</sup>	–0.04
Albumin <sup>b</sup>	41.8 $\pm$ 3.8	41.0 $\pm$ 3.8 <sup>i</sup>	43.2 $\pm$ 3.3 <sup>i</sup>	0.34 <sup>b</sup>	0.23
High titre antibodies $\geq$ 100 IU/mL, yes <sup>h</sup>	4 (5.8)	1 (2.3)	3 (12.0)	–0.17	–0.56 <sup>b</sup>
Faecal calprotectin <sup>b</sup>	102.0 (65–368)	368.0 (102.0–825.0)	68.0 (36.0–355.0)	–1.00	–0.26
Type of imaging					
CT	17 (24.6)	12 (27.3)	5 (20.0)	—	—
MRI	52 (75.4)	32 (72.7)	20 (80.0)	—	—
AC (cm)	97.2 $\pm$ 13.0	98.3 $\pm$ 12.8	95.2 $\pm$ 13.3	–0.17	–0.26
VFA (cm <sup>2</sup> )	113.2 $\pm$ 94.0	121.5 $\pm$ 92.3	98.6 $\pm$ 96.8	–0.30 <sup>b</sup>	–0.34
SFA (cm <sup>2</sup> )	184.8 $\pm$ 97.7	193.0 $\pm$ 100.5	170.4 $\pm$ 92.9	–0.17	–0.14
TFA (cm <sup>2</sup> )	298.0 $\pm$ 153.5	314.5 $\pm$ 146.8	269.0 $\pm$ 163.5	–0.27	–0.25
SMA (cm <sup>2</sup> )	152.2 $\pm$ 42.7	155.3 $\pm$ 45.6	146.8 $\pm$ 37.2	–0.03	–0.20
VFI (cm <sup>2</sup> /m <sup>2</sup> )	38.5 $\pm$ 31.2	41.1 $\pm$ 30.0	34.1 $\pm$ 33.4	–0.35 <sup>b</sup>	–0.30
SMI (cm <sup>2</sup> /m <sup>2</sup> )	51.3 $\pm$ 12.4	52.4 $\pm$ 13.2	49.3 $\pm$ 11.1	–0.16	–0.17
VFA:SMA ratio	0.7 $\pm$ 0.6	0.8 $\pm$ 0.5	0.7 $\pm$ 0.7	–0.34 <sup>b</sup>	–0.25

Data are presented as n (%), mean  $\pm$  SD, or median (IQR) unless otherwise specified.

AC, abdominal circumference; BMI, body mass index; CD, Crohn's disease; CRP, C-reactive protein; IQR, interquartile range; PSC, primary sclerosing cholangitis; SFA, subcutaneous fat area; SMA, skeletal muscle area; SMI, skeletal muscle index; TFA, total fat area; TNF $\alpha$ , tumor necrosis factor-alpha; VFA, visceral fat area; VFI, visceral fat index.

<sup>a</sup>Spearman correlation.

<sup>b</sup>Significant for *P* value < 0.05.

<sup>c</sup>Any metabolic risk factor including any of the following: hyperlipidemia, hypertension, type 2 diabetes mellitus, ischemic heart disease, and fatty liver.

<sup>d</sup>Extraintestinal manifestations including any of the following: PSC, erythema nodosum, uveitis, scleritis, pyoderma gangrenosum, and inflammatory arthritis.

<sup>e</sup>Presence of other inflammatory condition includes any of the following: rheumatoid arthritis, psoriasis, ankylosing spondylitis, vasculitis, or coeliac disease.

<sup>f</sup>Secondary loss of response (anti-TNF $\alpha$  failure) defined as requiring reinduction, dose increase or shortening of interval, greater than or equal to two steroid courses a year courses a year, a switch out of class, or requiring surgery.

<sup>g</sup>Measured within a month of the trough level.

<sup>h</sup>Level of >100 AU/mL considered high titre/neutralizing level of antibody.

<sup>i</sup>Significantly different between infliximab and adalimumab group, *P* = 0.01.

CT and MRI measurements have shown to produce similar results (9).

All images were manually segmented using the ImageJ free-hand tool with a Microsoft Surface Pen on a Microsoft Surface Pro 4. The AC measurement excluded stoma bags. Where the body edge was excluded from the field of view, no attempt was made to extrapolate missing tissue, potentially underestimating AC and SFA. VFA excluded large mesenteric vessels, mesenteric nodes, bowel loops, and solid organs. In cases where there was an abdominal wall hernia or stoma site, the herniated fat was included in the VFA and excluded from the SFA measurements.

### Statistical methods

Descriptive statistics were used to summarize baseline demographic and clinical characteristics. Categorical data were described as proportions and were compared across groups with

Pearson  $\chi^2$  tests. Normally distributed continuous data were described with means  $\pm$  SD and compared across groups with Student *t* tests. Non-normally distributed data were described with medians and interquartile ranges (IQRs) and compared across groups with a Mann-Whitney *U* test. Univariate associations between body composition areas and drug levels were first assessed with the Spearman rank correlation coefficient (*R*s). The multivariate linear regression method was used to assess the impact of various body compartment area measurements individually on IFX and ADA trough levels after adjusting for age, sex, CRP and albumin level, antibody seropositivity (>100 AU/mL), and concurrent immunomodulator use by inserting each compartment area of interest into the model, one at a time. Time to SLOR was compared using the Kaplan-Meier statistics. Univariate and multivariate Cox regression analyses corrected for Montreal age at diagnosis,

trough levels, smoking status, and antibody seropositivity (>100 AU/mL), and concurrent immunomodulator use determined if any of the body compartment areas were independent predictors of SLOR by inserting each compartment area of interest into the model, one at a time. IBM SPSS v25.0 was used for statistical analysis and a 2-sided *P* value less than 0.05 was considered statistically significant.

### Ethical considerations

The project was approved by the South Metropolitan Area Health Service Human Research Ethics committee.

## RESULTS

### Baseline characteristics

The clinical characteristics of 69 patients with CD that met the inclusion criteria (Figure 1) are presented in Table 1. Forty-two patients (60.9%) were men, and the mean age in years was  $43.5 \pm 16.2$ . The mean BMI of the cohort was  $26.9 \pm 5.1$  with 13 patients (18.8%), having at least one metabolic risk factor. An ileocolonic disease distribution ( $n = 38$ , 55.1%) and a stricturing disease behavior ( $n = 36$ , 52.2%) were the predominant phenotype, whereas 18 patients (26.1%) had perianal disease.

Disease activity was present at the time of acquiring the trough level, with a median Harvey-Bradshaw index score of 12 (IQR 10–15) and a fecal calprotectin level of 102  $\mu\text{g/g}$  (IQR 65–368). IFX was administered in 44 patients (63.8%) and ADA in 25 patients (36.2%). The median trough levels and IQRs for IFX and

ADA were 4.9  $\mu\text{g/mL}$  (1.6–8.9) and 6.1  $\mu\text{g/mL}$  (3.1–10.8), respectively. The median duration from induction to the measured trough level for IFX was 11 months (IQR 4.25–28.25) and for ADA was 8 months (IQR 2.0–23.0). Four patients (5.8%) had antibodies present, and all had high titre (>100 AU/mL) antibodies. The median duration in months between acquiring the trough level and the CT/MRI was 2.1 (0.9–3.4). Thirty-six patients (52.2%) met the criteria for SLOR with a median duration from induction to SLOR of 20.2 months (IQR 13.8–35.6). The median duration between the CT/MRI to SLOR was 11.9 months (IQR 3.0–18.8). Twenty-two patients (31.9%) had either their AC or SFA measurements underestimated. Of the 20 patients who had an underestimated AC, 14 patients (70%) were treated with IFX, and of the 21 patients who had an underestimated SFA, 15 (71.4%) were treated with IFX.

There were no significant differences between IFX- and ADA-treated patients regarding any baseline clinical characteristic apart from serum albumin level ( $41.0 \text{ g/L} \pm 3.8$  vs  $43.2 \text{ g/L} \pm 3.3$  for IFX and ADA, respectively,  $P = 0.01$ ). Most patients had a CT/MRI performed because of having symptoms and/or biochemical markers that suggested active disease (63.6%); however, most patients had an anti-TNF $\alpha$  trough level taken proactively to optimize the performance of the biologic (59.4%) (Table 1).

The BMI of each patient was compared against body and compartment area measurements (Figure 2). The measurement with the strongest correlation with BMI was AC ( $R_s = 0.86$ ,  $P <$

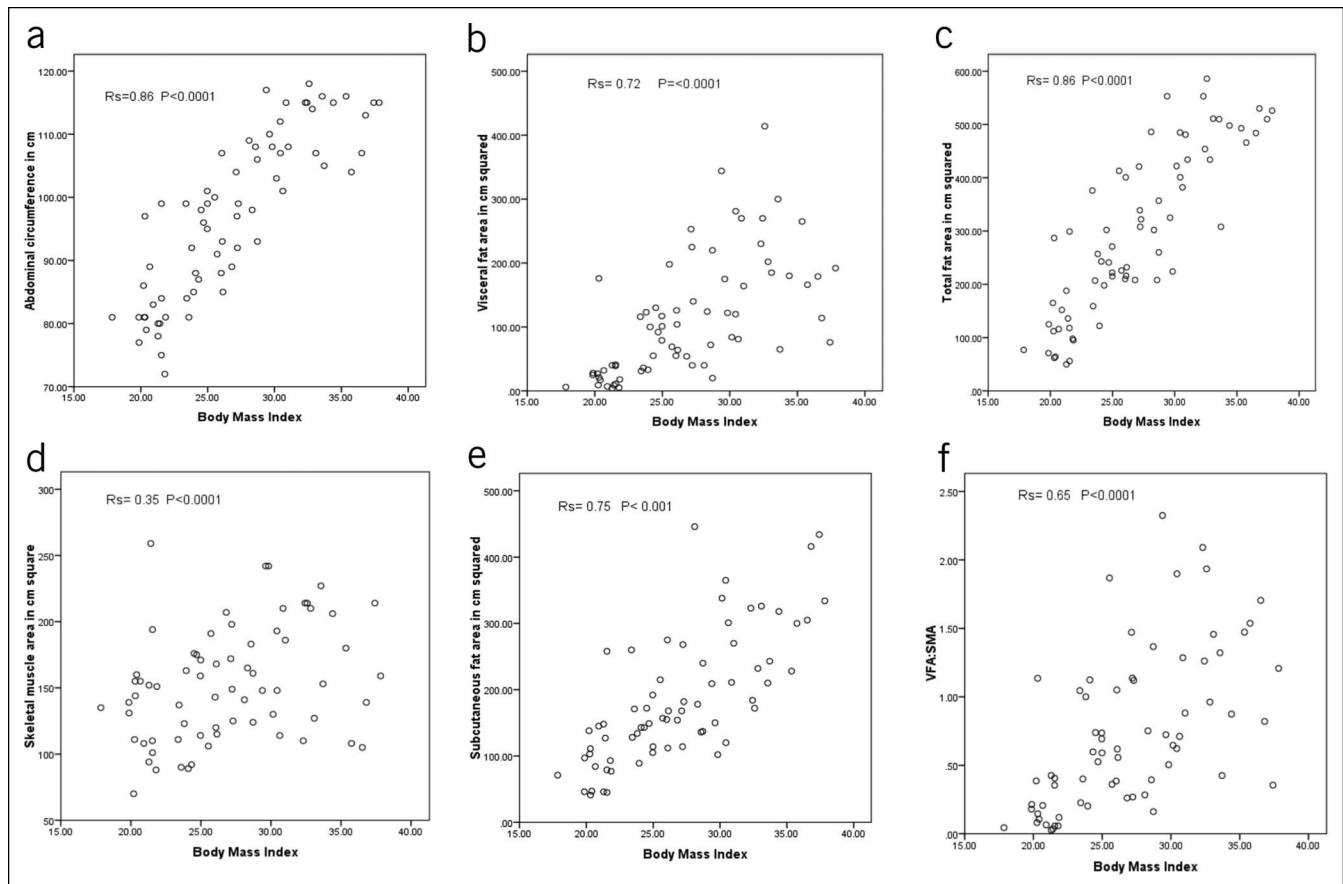


Figure 2. Correlation of body compartment areas with body mass index (a–f).



0.0001) and TFA ( $R_s = 0.86$ ,  $P < 0.0001$ ). SMA displayed the weakest correlation with BMI ( $R_s = 0.35$ ,  $P = 0.003$ ); however, when corrected for height (skeletal muscle index), a better, albeit moderate correlation ( $R_s = 0.50$ ,  $P < 0.0001$ ) was seen. Both VFA and visceral fat index (VFI) correlated well with BMI ( $R_s = 0.72$ ,  $P < 0.0001$  and  $R_s = 0.73$ ,  $P < 0.0001$ , respectively); however, the correlation between AC and VFI and TFA was even better ( $R_s = 0.82$ ,  $P < 0.0001$  and  $R_s = 0.91$ ,  $P < 0.0001$ , respectively).

#### Correlation of baseline characteristics with anti-TNF $\alpha$ trough levels

IFX trough levels were negatively correlated with the incidence of SLOR ( $R_s = -0.55$ ), CRP level ( $R_s = -0.38$ ), VFA ( $R_s = -0.30$ ), VFI ( $R_s = -0.35$ ), and VFA:SMA ratio ( $R_s = -0.34$ ), whereas ADA trough levels were negatively correlated with hemoglobin level ( $R_s = -0.54$ ) and the presence of high titre antibodies against ADA ( $R_s = -0.56$ ) (Table 1). By contrast, IFX trough levels were positively correlated with active smoking ( $R_s = 0.31$ ), the time to SLOR in months ( $R_s = 0.31$ ), and serum albumin level ( $R_s = 0.34$ ). There were no variables that positively correlated with ADA trough levels.

#### Body compartment associations with trough levels

The body compartment measurements that remained as significant predictors for IFX trough levels after multivariate adjustment were VFA ( $-0.02$  [ $-0.04$ ,  $-0.003$ ]  $P = 0.03$ ), VFI ( $-0.07$  [ $-0.12$ ,  $-0.01$ ],  $P = 0.02$ ), and the VFA:SMA ratio ( $-3.81$  [ $-7.13$ ,  $-0.5$ ],  $P = 0.03$ ) (Table 2). BMI itself was not associated with IFX trough levels ( $-0.23$  [ $-0.52$ ,  $0.06$ ],  $P = 0.11$ ). For ADA trough levels (see Supplementary Table 1, Supplementary Digital Content 1, <http://links.lww.com/CTG/A374>), no associations were found in the univariate, age- and gender-adjusted, and multivariate-adjusted analyses between trough levels and body compartment areas or BMI.

#### Body compartment associations with time to SLOR

For both IFX- and ADA-treated patients, there was a trend toward a significant separation of drug survival curves between the tertiles of VFI on the Kaplan-Meier analysis ( $P = 0.09$  and  $P =$

$0.06$  for IFX and ADA, respectively; Figure 3). The median time to SLOR for each category of VFI ( $<30$ ,  $30-60$ , and  $>60$   $\text{cm}^2/\text{m}^2$ ) was 78.0, 43.2, and 16.8 months for IFX-treated patients and 36.6, 39.8, and 23.9 months for ADA-treated patients, respectively. On multivariate Cox regression analysis for IFX-treated patients, no body compartment elements, including BMI remained predictive for SLOR (see Supplementary Table 2, Supplementary Digital Content 2, <http://links.lww.com/CTG/A375>); however, in ADA-treated patients, the body compartment measurements that independently determined SLOR were AC (1.08 [1.01, 1.16],  $P = 0.02$ ), SFA (1.016 [1.005, 1.026],  $P = 0.004$ ), TFA (1.009 [1.002, 1.016],  $P = 0.011$ ), the highest tertile of VFI ( $>60$   $\text{cm}^2/\text{m}^2$ ) (16.02 [1.58, 162.62],  $P = 0.02$ ), VFA:SMA ratio (3.45 [1.04, 11.50],  $P = 0.04$ ), and BMI (1.30 [1.06, 1.59],  $P = 0.01$ ) (Table 3).

## DISCUSSION

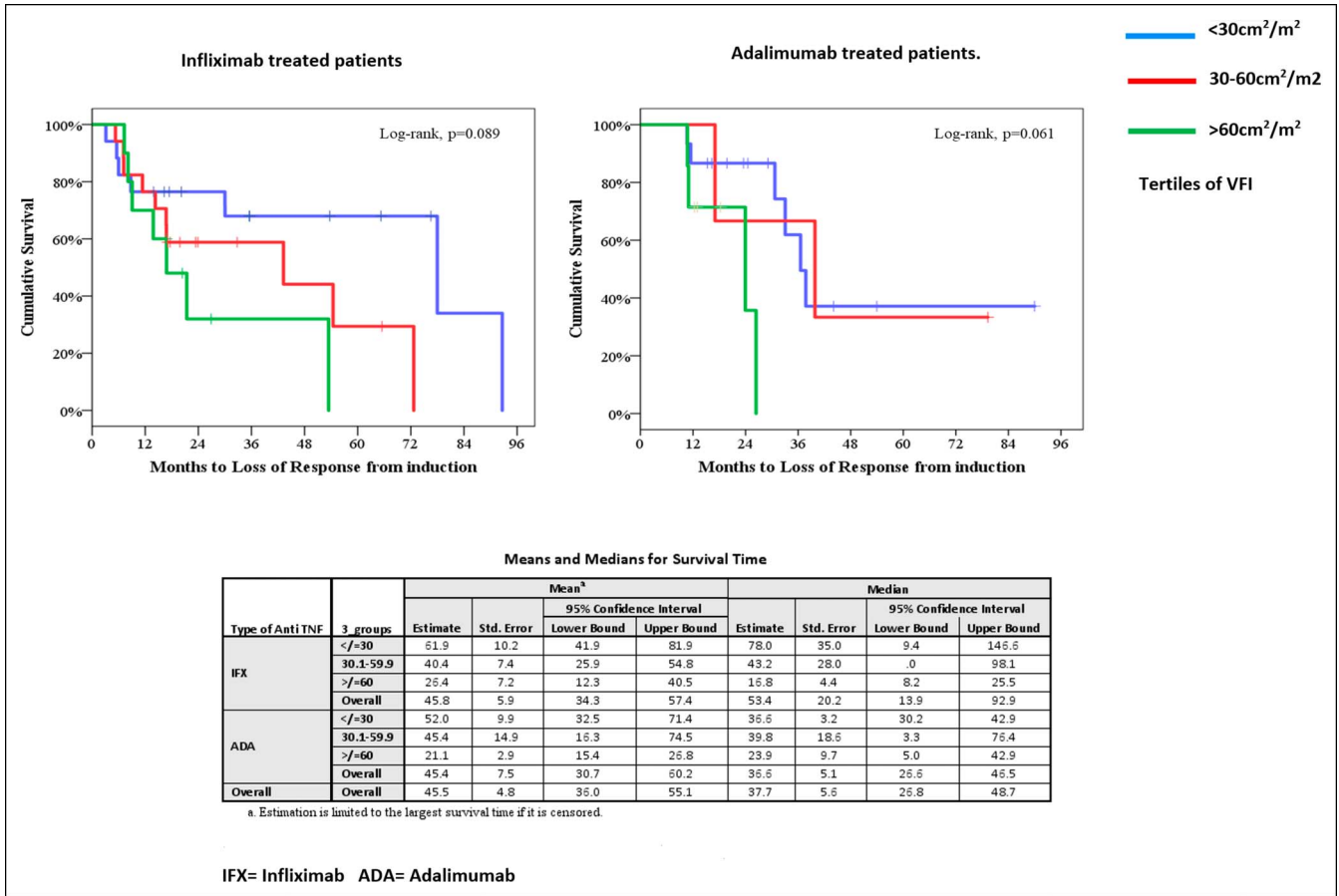
TNF $\alpha$ , previously known as “cachexin,” suppresses appetite and a prolonged exposure and can result in cachexia, a wasting syndrome, seen in many inflammatory conditions. Blocking TNF $\alpha$  reverses this cachexic process. Prospective body composition studies in rheumatology (10) and patients with IBD (11) have demonstrated a disproportionate accumulation of adipose tissue compared with muscle and bone over time in patients on long-term anti-TNF $\alpha$  treatment, compounding the pre-existing problem of obesity seen in both the general population and patients with IBD (12). To our knowledge, our study is the first to demonstrate the impact of body composition on anti-TNF $\alpha$  trough levels and secondary loss of response. Our data showed that IFX, but not ADA trough levels, were significantly correlated in an inverse relationship with VFA, VFI, and the VFA:SMA ratio and that high adiposity measurements are directly correlated with a higher risk of experiencing secondary loss of response in ADA-treated patients.

The inverse association between VFA and IFX trough levels is consistent with the work by Dotan et al. (13), who showed that an increased body mass was associated with a proportional increase in the volume of distribution in central and peripheral compartments, thereby increasing the clearance of IFX (13). Our data suggest that the increased volume of distribution is mainly the consequence of high adiposity, particularly visceral adiposity.

**Table 2.** Univariate, age- and gender-adjusted, and multivariate<sup>a</sup>-adjusted predictors for infliximab trough level

Body composition areas	Infliximab only (n = 44)					
	Unadjusted	P	Age- and gender-adjusted	P	Multivariate-adjusted	P
Abdominal circumference	-0.06 (-0.17, 0.05)	0.28	-0.07 (-0.18, 0.05)	0.28	-0.05 (-0.17, 0.07)	0.42
Visceral fat area (VFA)	-0.02 (-0.03, 0.000)	0.04	-0.02 (-0.04, -0.004)	0.02	-0.02 (-0.04, -0.003)	0.03
Subcutaneous fat area	-0.01 (-0.02, 0.01)	0.30	-0.01 (-0.02, 0.01)	0.38	-0.01 (-0.02, 0.01)	0.50
Total fat area	-0.01 (-0.02, 0.000)	0.047	-0.01 (-0.02, 0.001)	0.07	-0.01 (-0.02, 0.002)	0.10
Skeletal muscle area (SMA)	-0.002 (-0.03, 0.03)	0.92	-0.03 (-0.08, 0.02)	0.22	-0.03 (-0.08, 0.02)	0.24
Visceral fat area corrected for stature	-0.05 (-0.10, -0.01)	0.01	-0.06 (-0.12, -0.01)	0.01	-0.07 (-0.12, -0.01)	0.02
Skeletal muscle area corrected for stature	-0.04 (-0.14, 0.07)	0.51	-0.10 (-0.23, 0.03)	0.13	-0.1 (-0.23, 0.04)	0.17
VFA/SMA	-3.40 (-6.16, -0.65)	0.02	-3.76 (-6.89, -0.63)	0.02	-3.81 (-7.13, -0.50)	0.03
Body mass index ( $\text{kg}/\text{m}^2$ )	-0.25 (-0.53, 0.03)	0.08	-0.26 (-0.54, 0.02)	0.07	-0.23 (-0.52, 0.06)	0.11

<sup>a</sup>Multivariate regression adjustment for age, sex, C-reactive protein (mg/mL), albumin (g/L), antibody seropositivity ( $>100$  IU/mL), and concurrent immunomodulator use (thiopurines of methotrexate).



**Figure 3.** Kaplan-Meier survival analyses for patients treated with infliximab (IFX) or adalimumab (ADA) differentiated by tertiles of visceral fat index (VFI). The table includes the mean and median estimates for time to secondary loss of response for each tertile of visceral fat index in (cm<sup>2</sup>/m<sup>2</sup>).

Apart from determining the central volume of distribution, visceral fat is also a metabolically active organ capable of secreting a variety of cytokines and adipokines. Mesenteric visceral fat has a

predominance of proinflammatory macrophages that secrete inflammatory cytokines such as TNF $\alpha$  and interleukin-1 (14). Adipocytes also produce other proinflammatory cytokines such

**Table 3.** Univariate and multivariate analysis<sup>a</sup> for determinants of secondary loss of response in adalimumab patients

	Adalimumab (n = 25)					
	Unadjusted	P	Age- and gender-adjusted	P	Multivariate regression	P
Abdominal circumference	1.04 (0.99, 1.10)	0.11	1.07 (0.99, 1.16)	0.11	<b>1.08 (1.01, 1.16)</b>	<b>0.02</b>
Visceral fat area (VFA)	1.004 (0.998, 1.011)	0.19	1.006 (0.996, 1.017)	0.23	1.006 (0.998, 1.015)	0.15
Subcutaneous fat area	1.010 (1.002, 1.019)	0.01	1.009 (1.000, 1.019)	0.045	1.016 (1.005, 1.026)	0.004
Total fat area	1.003 (1.001, 1.012)	0.02	1.006 (1.000, 1.013)	0.05	1.009 (1.002, 1.016)	0.01
Skeletal muscle area (SMA)	0.99 (0.97, 1.01)	0.14	0.98 (0.96, 1.01)	0.18	0.98 (0.95, 1.01)	0.14
Visceral fat area corrected for stature (VFI)	1.02 (0.98, 1.04)	0.10	1.02 (0.99, 1.05)	0.16	1.024 (0.999, 1.051)	0.07
VFI (<30 cm <sup>2</sup> /m <sup>2</sup> )	Reference	—	Reference	—	Reference	—
VFI (30–60 cm <sup>2</sup> /m <sup>2</sup> )	0.96 (0.19, 4.89)	0.97	0.97 (0.12, 7.93)	0.98	0.57 (0.02, 15.86)	0.74
VFI (>60 cm <sup>2</sup> /m <sup>2</sup> )	5.30 (1.11, 25.36)	0.04	3.86 (0.51, 29.26)	0.19	16.02 (1.58, 162.62)	0.02
Skeletal muscle area corrected for stature	0.98 (0.93, 1.04)	0.49	0.97 (0.90, 1.04)	0.33	0.98 (0.89, 1.07)	0.64
VFA/SMA	2.61 (1.02, 6.69)	0.046	2.67 (0.75, 9.49)	0.13	3.45 (1.04, 11.50)	0.04
Body mass index (kg/m <sup>2</sup> )	1.17 (1.02, 1.34)	0.03	1.13 (0.97, 1.32)	0.11	1.30 (1.06, 1.59)	0.01

<sup>a</sup>Multivariate regression adjustment for Montreal age groups (A1  $\leq$  16, A2 = 17–40, A3 > 40), trough level, smoking status (active or inactive at time of CT/MRI), antibody seropositivity (>100 IU/mL), and concurrent immunomodulator use.

as interleukin-6; chemokines such as C-C motif (chemokine ligand 2); and adipokines such as leptin and resistin (15). These latter adipokines can in turn induce the innate immune response and influence the expression of several inflammatory mediators (14,15). Thus, visceral fat acts as an immunologically active “anti-TNF $\alpha$  sink.”

Our data showed that although BMI correlated well with each body compartment measurement, it was not an independent determinant of IFX or ADA trough levels on the multivariate linear regression analysis. By contrast, measures of adipose stores were significant determinants of IFX trough level, but not for ADA levels, likely because of the small sample size. By comparison, the PANTS study also found that BMI was not significantly associated with the week 14 or 54 IFX drug concentrations, but was for ADA drug concentrations (16). This discrepancy may be explained by IFX’s weight-based dosing compared with ADA’s fixed-dosing regimen. Taken together, it does appear that body mass influences dosing, however fat mass may provide *additional* guidance for dosing in obese individuals, such that a dose beyond 5 mg/kg to maintain therapeutic levels may be required in these patients.

In our cohort, BMI correlated well with the measures of adipose stores and AC, but weakly with SMA ( $R_s = 0.35$ ), indicating that those with a high BMI were more fat than muscular. Ding et al. (17) also showed that BMI correlated poorly with lean mass in their cohort of 106 anti-TNF $\alpha$ -treated patients with IBD ( $R^2 = 0.15$ ,  $P = 0.54$ ). Patients with IBD are known to have a body composition that is higher in ratio of visceral fat to muscle mass in population-based studies (18,19). Taken together, our results highlight the fact that BMI is a poor discriminant of true body composition in patients with IBD but is a reasonable surrogate marker for high adiposity. Our data also showed that AC displayed an even better correlation with total and visceral fat stores, which is easily measurable in clinic.

High levels of adiposity have been shown to correlate with poorer control of disease activity in both IBD and rheumatology literature (20–22). Likewise, we found that ADA-treated patients had a higher risk of developing SLOR with increasing values of AC, SFA, TFA, VFI tertile, VFA:SMA ratio, and BMI after multivariate adjustment. In IFX-treated patients, no single body compartment was independently predictive for SLOR. The discrepancy observed between ADA- and IFX-treated patients for associations between adipose areas and SLOR may again be attributed to the fact that IFX dosing is weight-based, whereas ADA dosing is fixed. A significant collinear relationship exists between body mass and each of the adipose compartments (TFA, SFA, and VFA) (Figure 2) and in turn between VFA and trough level, which is known to directly affect SLOR. ADA, on the other hand, does not have the issue of body mass confounding the administered dose and hence the trough level. In the PANTS study, remission status was similarly not associated with BMI in IFX-treated patients ( $P > 0.05$ ); however, in ADA-treated patients, BMI was associated with an increased risk of week 54 nonremission status for overweight (hazard ratio = 2.31 [1.28–4.25],  $P = 0.006$ ) and obese patients (hazard ratio = 3.42 [1.51–8.43],  $P = 0.005$ ) (16). Madsen et al. (23), on the other hand, found that in 210 patients with IBD, BMI did not predict a SLOR to anti-TNF $\alpha$  agents overall. A major shortcoming of this study, however, was that patients were not further subanalysed by the type of anti-TNF $\alpha$  within each IBD subtype (23), which we know have differing response rates. Our results

and those of the PANTS study affirm that patients with a higher body mass, and perhaps those with a higher adiposity level (as our data suggests) are likely to derive a greater benefit from weight-based rather than fixed-dosing regimens for maintaining clinical response.

There were a few limitations to acknowledge in our study. First, the small sample size of the ADA treatment group may have introduced a type II error to the negative results seen in the primary outcome (trough level) for ADA-treated patients. Despite the small numbers, we feel that the positive signals that have emerged from our data warrant attention and further investigation in prospective studies. Second, we relied on cross-sectional imaging to estimate body composition, rather than measurements from whole-body dual energy x-ray absorptiometry (DEXA). There is notable evidence that supports the validity of relying on the former method (9). Kullberg et al. (9), demonstrated high correlation values for the measurements of adipose tissue compartments between CTs and MRIs ( $r = 0.998$ ), CTs and DEXAs ( $r = 0.990$ ), and MRIs and DEXAs ( $r = 0.979$ ). Third, approximately one-third of the cohort had their SFA and/or AC measurements underestimated because these parameters were excluded from the imaging field of view. These underestimations particularly affected those who were prescribed IFX and may have skewed the results in favor of visceral fat being the main determinant of trough levels in IFX-treated patients (as opposed to the other adipose compartments). Despite the underestimation, it is notable that AC, TFA, and SFA were still found to be independent predictors of SLOR in ADA-treated patients. Finally, because of the retrospective nature of the study, selection bias may have been introduced; CT/MRI scans were more likely to have been performed in patients who had symptoms rather than for checking response to therapy proactively. The evident selection bias may have made our results less generalizable; however, adjustments were made for established risk factors affecting SLOR and trough levels such as inflammatory burden.

A body composition high in visceral fat is associated with a lower IFX trough level. A high AC and a body composition that is high in measured total, subcutaneous, and visceral fat is associated with an increased risk of developing SLOR in ADA-treated patients. Lifestyle interventions to prevent or reverse a high adipose to muscle ratio, early in the treatment course with anti-TNF $\alpha$  agents, and/or the commencement of a higher loading dose may promote anti-TNF $\alpha$  drug persistence. Prospective studies are required to validate these hypotheses.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Lena Thin, MBBS, FRACP, MCLinRes.

**Specific author contributions:** L.T.: involved in the conception and design of the study, drafting the article, statistical analysis, and revising it critically for important intellectual content and is also the guarantor of the article and a co-first author. Z.L.: involved in the design, data extraction, drafting the article, and analysis of data. C.J.W.: measured the body compartment areas, involved in the analysis, drafting the article, and revising it critically. R.W.: provided statistical support and revised the article critically. All authors approved the final version to be submitted and the order of the authors listed.

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**Potential competing interests:** None to report.



## Study Highlights

### WHAT IS KNOWN

- ✓ A high body mass index (BMI) is known to adversely affect antitumor necrosis factor- $\alpha$  (TNF $\alpha$ ) trough levels and secondary loss of response in patients with Crohn's disease; however, the role of fat in high BMI patients is unknown.

### WHAT IS NEW HERE

- ✓ A high visceral adipose burden is associated with lower infliximab trough concentrations, and a high total fat burden is associated with an increased risk of secondary loss of response in adalimumab-treated patients.

### TRANSLATIONAL IMPACT

- ✓ Diet and exercise to prevent or reverse obesity, and/or administering a higher loading dose for obese patients may need to be considered at the commencement of anti-TNF $\alpha$  therapy.

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