Treatment Failure of TNF- Inhibitors in Obese Patients With Inflammatory Bowel Disease—A Cohort Study

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Background: In treatment of inflammatory bowel disease (IBD) with anti–tumor necrosis factor–α agents (anti-TNF-α), obesity has been suspected as a cause of accelerated loss of response (LOR). We sought to determine whether overweight IBD patients have accelerated LOR when treated with anti-TNF-α agents, compared with normal weight IBD patients.

Methods: We identified a cohort of adult IBD patients treated with anti-TNF-α agents at a Danish university hospital. Patients were grouped according to body mass index (BMI), and our main outcome was time to LOR. We performed survival analyses on LOR and calculated hazard ratios (HRs) with the normal weight group as the reference, while adjusting for confounders.

Results: Of 210 eligible patients, 92 (44%) experienced LOR. One hundred eighty patients were treated with infliximab and 30 with adalimumab, 114 (54%) were normal weight, 51 (24%) were overweight, and 45 (21%) were obese. Regression analysis produced the following adjusted HRs, compared with the normal weight group: overweight 0.89 (95% confidence interval [CI], 0.51–1.56) and obese 1.31 (95% CI, 0.76–2.24), thus showing no statistically significant association between BMI and time to LOR. Subgroup analyses produced similar results, except for obese ulcerative colitis patients having an adjusted HR of 2.42 (95% CI, 1.03–5.70).

Conclusions: In IBD patients treated with anti-TNF-α agents, we found no overall association between increased BMI and accelerated LOR.

Key Words: IBD, obesity, anti–tumor necrosis factor–α agents, Crohn's disease, ulcerative colitis

INTRODUCTION

The introduction of anti–tumor necrosis factor–α (anti-TNF-α) agents in the late 1990s has revolutionized the management of inflammatory bowel disease (IBD). Unfortunately, 13%–40% of IBD patients are primary nonresponders to anti-TNF-α agents, and approximately one-third of patients will lose response over time.[1–6] Obesity has been suggested to be a predictor for loss of response (LOR). However, this has mostly been studied in other autoimmune diseases such as rheumatoid arthritis[7–9] and spondyloarthritis.[10, 11]

In the case of IBD, only a few smaller studies have addressed this issue directly, some of which suggest that obesity is associated with accelerated LOR.[12–14] There is no consensus on whether this association exists both for weight-adjusted anti-TNF-α agents—for example, infliximab (IFX)—and for agents where dosing is fixed, for example, adalimumab (ADA).[12–14] Correspondingly, there is no consensus on whether obesity is a predictor of an adverse prognosis in IBD.[15–19]

In a Danish cohort of IBD patients treated with anti-TNF-α agents, we sought to determine whether overweight patients have accelerated LOR for anti-TNF-α agents, compared with normal weight patients.

METHODS

This is an observational cohort study of adult IBD patients treated with anti-TNF-α agents at the Department of Medical Gastroenterology, Odense University Hospital, Denmark, in the period between January 1, 2003, and December 31, 2015. Patients were classified according to body mass index (BMI): underweight (BMI < 18.5), normal weight (BMI, 18.5–25), overweight (BMI, 25–30), and obese (BMI > 30).[20] We compared time to LOR between these groups. Patients were included if they were at least age 18 years at treatment initiation and were treated for Crohn's disease (CD) or ulcerative colitis (UC) with anti-TNF-α agents. In the analysis, we excluded patients with no recorded information on weight or height, patients with BMI <18.5, patients who had previously received anti-TNF-α agent treatment, patients classified as

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primary nonresponders to anti-TNF-α therapy, and patients who discontinued treatment during or immediately after induction for other reasons. We defined primary nonresponse as stop of treatment due to lack of effect within 16 weeks after the first treatment.[21]

We identified the cohort by manually reviewing medical records, retrieving information on IBD subtype, course of the disease, date of anti-TNF-α agent treatment initiation, choice of anti-TNF-α agent, treatment response, time and reason for discontinuation, treatment intensification (ie, dose increase or reduced treatment interval), surgery due to IBD, smoking status, sex, height, age, and weight at treatment initiation. For all patients, we retrieved information on the extent, behaviour, and activity of the disease, following the Montreal classification.[22]

We obtained data on concurrent prescription medication from the Odense Pharmaco-Epidemiological Database (OPED), which is a database on subsidized prescriptions for the inhabitants of the Region of Southern Denmark.[23] Linkage of the data was performed using the personal identification number, which is a unique identifier assigned to all Danish individuals.[24] We obtained prescription data on glucocorticoids for systemic use, 5-ASA, azathioprine, and methotrexate. The main outcome was time to LOR after initiation of anti-TNF-α treatment, with LOR defined by dose increase, reduced treatment interval, surgery due to IBD, or discontinuation of anti-TNF-α agent due to nonsatisfactory treatment response. If a patient experiences a flare in the disease during anti-TNF-α agent treatment, the standard approach is to increase the dose or to reduce the treatment interval.[21] Therefore, we included dose increase and reduction of treatment interval as proxies for LOR. Time to LOR was calculated from date of first treatment with anti-TNF-α agent to first date with 1 of the events mentioned above. Using Cox regression, we calculated hazard ratios for the 3 BMI categories: normal weight, overweight, and obese, with the normal weight group as the reference. In further analysis, we adjusted for age, sex, and smoking status. Finally, we performed an extended analysis with adjustment for age, sex, smoking status, concurrent medication, former bowel resection, IBD subtype, and type of anti-TNF-α.

All analyses were performed using STATA, release 14.1 (StataCorp, College Station, TX, USA).

Ethical Considerations

The Danish Data Protection Agency approved the study (file number 2012-58-0018). The Danish Health Authority approved the study (case number 3-3013-1116/2). Approval from the Ethics Committee was not required according to Danish law.

RESULTS

We identified a cohort of 374 patients. Forty-four patients (12%) were excluded due to primary nonresponse to treatment. In 57 patients (15%), treatment was discontinued during or just after completing induction treatment for reasons other than nonresponse. These 57 patients were mostly treated when experience with anti-TNF-α treatment was limited and maintenance treatment was not yet established as routine practice. In 37 patients (10%), we had no information on BMI. Eighteen patients were excluded due to BMI <18.5. Two hundred ten patients were eligible for analysis (Fig. 1), with a median follow-up (interquartile range) of 9.6 (5.4–15.6) months. At initiation of anti-TNF-α treatment, 54% of the patients were normal weight, 24% overweight, and 21% obese, (Table 1). IFX was used in 86% of patients, and ADA was used in 14% of patients (Table 1). Among the 210 patients included in the analysis, 92 patients (44%) experienced LOR during 247 person-years at risk. The LOR was distributed among the BMI groups as follows: normal weight 53 (47%), overweight 17 (33%), and obese 22 (49%) (Table 1). In 43 (20%) patients, treatment was discontinued due to side effects or infection. Thirty-nine patients (19%) discontinued treatment due to long-lasting remission. These subjects were censored in the survival analysis.

Hazard ratios for overweight and obese patients were 0.90 (95% confidence interval [CI], 0.52–1.55) and 1.13 (95% CI, 0.69–1.87) compared with the normal weight category. Thus, none of the BMI categories showed a statistically significantly higher hazard ratio of LOR, compared with the normal weight category. Figure 2 shows the Kaplan-Meier plot of the 4 BMI categories from initiation of anti-TNF-α treatment to LOR. Adjusting for sex, age, and smoking status yielded only minor changes to the estimates, and the same applied to an extended adjustment (Table 2).

Stratification by IBD subtype and by type of anti-TNF-α treatment did not alter the results substantially, except for obese patients treated for UC, who had a crude hazard of 2.38 (95% CI, 1.05–5.42) (Table 2). We redid the subgroup analyses and included phenotype and severity for Crohn's disease and ulcerative colitis. This did not produce any discernible change in results.

The IFX subgroup showed a trend toward decreased time to LOR with increasing BMI, and this trend was more pronounced in the adjusted analyses (Table 2).

In a post hoc analysis, we included the patients categorized as primary nonresponders (PNR). This yielded only negligible changes of the results. The abovementioned trend in the IFX group was more pronounced when including PNR patients, but only reached statistical significance in the extended adjustment (Table 3; Supplementary Data). Also, we established a secondary end point in which LOR was based purely on patients undergoing surgery. We analyzed time from initiation of treatment to first surgery, either during treatment or after treatment discontinuation, regardless of reason for discontinuation. This produced 46 events of LOR (surgery) during 398 person-years at risk, the surgery events were distributed uniformly between BMI groups with crude hazard ratios of 1.01 (95% CI, 0.49–2.11) for overweight and 1.04 (95% CI, 0.50–2.16) for obese

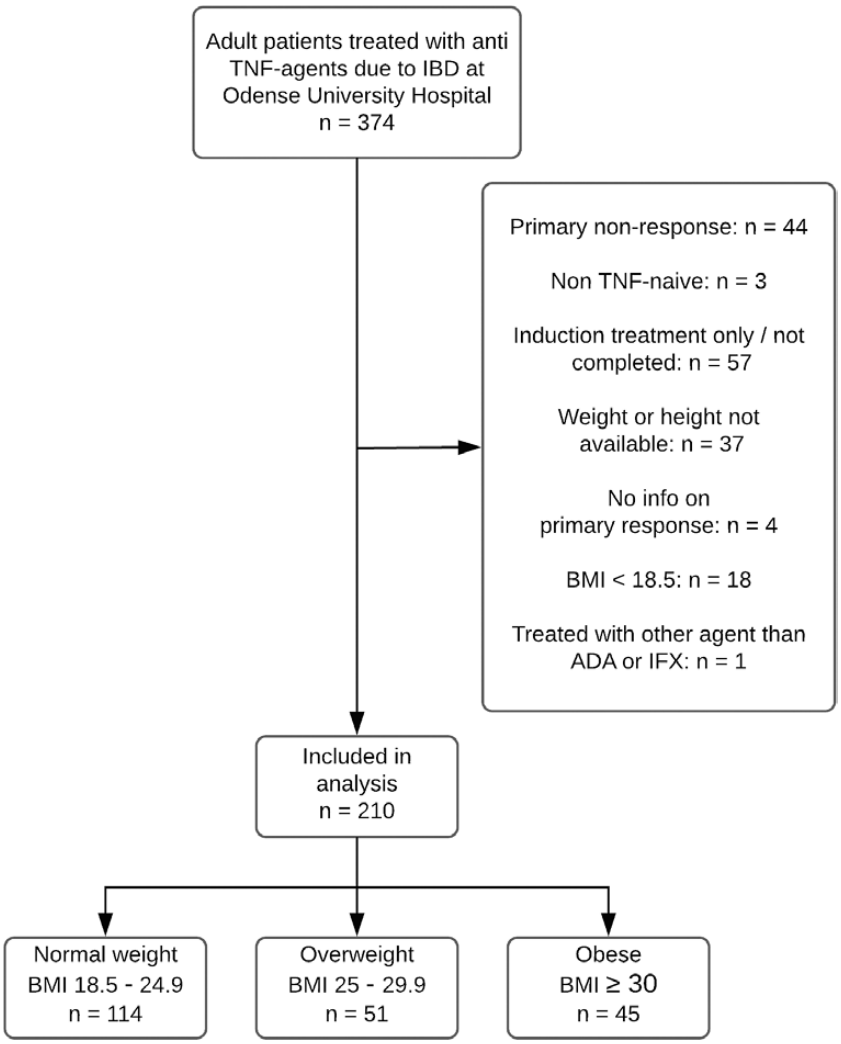

FIGURE 1. Study population. Eligibility criteria, exclusion criteria, and BMI distribution of 374 patients treated with anti-TNF-α agents for IBD at 1 Danish center, 2003–2015.

patients, compared with the normal weight group. Lastly, we evaluated the association between antiTNF exposure and LOR per unit of BMI, with BMI as a continuous variable instead of BMI categories. This approach did not reveal any new association between BMI and LOR, with each 1-point increase in BMI giving crude hazard ratios of 1.01 (95% CI, 0.97–1.04) for all IBD patients, 0.97 (95% CI, 0.93–1.02) for CD patients, and 1.08 (95% CI, 1.00–1.17) for UC patients. After adjustment for possible confounders, the UC patients had a hazard ratio of 1.11 (95% CI, 1.02–1.20) for each 1-point BMI increase.

DISCUSSION

In this large cohort study of adult IBD patients treated with anti-TNF-α agents, we found no overall association between overweight or obesity and time to LOR. However, when stratifying the patients in the disease entities UC and CD, we found an increased hazard ratio for LOR in obese UC patients. Identical results were found when the association was evaluated with BMI as a continuous variable instead of BMI categories.

For a drug with conventional first-order kinetics, the maintenance dose is independent of the volume of distribution; that is, obese patients should have the same daily dose in mg as normal weight patients. However, the pharmacokinetic properties of anti-TNF-α agents in IBD patients are extremely complex, and possibly even more so in obesity. If indeed obesity plays a role in response to anti-TNF-α agents, possible explanations include a pro-inflammatory role of the adipose tissue.[25–28] We did not routinely perform therapeutic drug monitoring (TDM) on patients treated with anti-TNF-α agents. TDM data could have been useful in this study to evaluate the effect of BMI on trough levels.

Having a high BMI does not necessarily mean having a large amount of body fat, and this study has no data on body

TABLE 1: Characteristics of 210 Adult IBD Patients Treated With Anti-TNF-α Agents, Divided Into Subgroups by BMI Category

	All Included	Normal weight	Overweight	Obese	
	n = 210	n = 114 (54%)	n = 51 (24%)	n = 45 (21%)	*P*
Age,[a] median (IQR), y	32 (24–44)	29 (23–43)	35 (27–44)	35 (29–45)	0.22
Years since diagnosis,[a] median (IQR)	3 (0–8)	4 (0–10)	3 (1–8)	3 (1–8)	0.34
Male sex, No. (%)	80 (38.1%)	41 (36.0)	22 (43.1)	17 (37.8)	0.67
Current smoker, No. (%)	63 (30.0%)	41 (36.0)	13 (25.5)	9 (20.0)	0.10
Anti TNF-α agent, No. (%)					
Infliximab	180 (85.7%)	96 (84.2)	47 (92.2)	37 (82.2)	0.30
Adalimumab	30 (14.3%)	18 (15.8)	4 (7.8)	8 (17.8)	0.30
IBD, No. (%)					
Crohn's disease	127 (60.5%)	72 (63.2)	30 (58.8)	25 (55.6)	0.65
Ulcerative colitis	74 (35.2%)	38 (33.3)	19 (37.3)	17 (37.8)	0.85
Unclassified IBD	9 (4.3%)	4 (3.5)	2 (3.9)	3 (6.7)	0.59
Concurrent drug use,[b] No. (%)					
5-ASA[c]	71 (33.8%)	34 (29.8)	20 (39.2)	17 (37.8)	0.40
Immunomodulator[d]	91 (43.3%)	50 (43.9)	18 (35.3)	23 (51.1)	0.31
Systemic steroid[e]	97 (46.2%)	48 (42.1)	30 (58.8)	19 (42.2)	0.12
CD, location, No. (%)					
Ileitis	26 (20.5%)	14 (19.4)	5 (16.7)	7 (28.0)	0.67
Colitis	34 (26.8%)	20 (27.8)	7 (23.3)	7 (28.0)	0.91
Ileocolitis	67 (52.8%)	38 (52.8)	18 (60.0)	11 (44.0)	0.48
CD, behavior, No. (%)					
Luminal	80 (63.0%)	40 (55.6)	23 (76.7)	17 (68.0)	0.47
Stricturing	27 (21.3%)	19 (26.4)	4 (13.3)	4 (16.0)	0.24
Fistulizing	20 (15.7%)	13 (18.1)	3 (10.0)	4 (16.0)	0.57
Perianal disease	22 (17.3%)	14 (19.4)	4 (13.3)	4 (16.0)	0.76
UC, location, No. (%)					
Ulcerative proctitis	11 (14.9%)	4 (10.5)	5 (26.3)	2 (11.8)	0.28
Leftsided	40 (54.1%)	22 (57.9)	8 (42.1)	10 (58.8)	0.69
Pancolitis	23 (31.1%)	12 (31.6)	6 (31.6)	5 (29.4)	0.96
UC, severity, No. (%)					
Chronic active	64 (86.5%)	34 (89.5)	16 (84.2)	14 (82.4)	0.98
Acute severe	10 (13.5%)	4 (10.5)	3 (15.8)	3 (17.6)	0.57
Prior bowel resection, No. (%)	35 (16.7%)	19 (16.7)	9 (17.6)	7 (15.6)	1.00
Prior fistula surgery/drainage, No. (%)	20 (9.5%)	12 (10.5)	4 (7.8)	4 (8.9)	0.95
Loss of response, No. (%)	92 (43.8%)	53 (46.5)	17 (33.3)	22 (48.9)	0.22

Abbreviation: IQR, interquartile range.
[a]Age at start of anti-TNF-α treatment.
[b]We defined concurrent medication as having retrieved a prescription within the last 3 months before initiation of anti-TNF-α treatment.
[c]ATC code: A07EC.
[d]ATC code: L04AX01 or L04AX03.
[e]ATC code: H02AB.

composition, that is, rate of body fat vs fat-free body mass; we only had access to data on BMI. A better test of the obesity-inflammation hypothesis would be a prospective study including measurements of body composition of the individual patient before treatment initiation.

We used dose escalation, that is, increased dose or decreased time between treatments, as a proxy marker for LOR. Dose escalation was based on a clinical assessment of whether the patient was losing treatment response. Thus, the validity of dose escalation as a proxy for LOR rests on the quality of the clinical assessment of

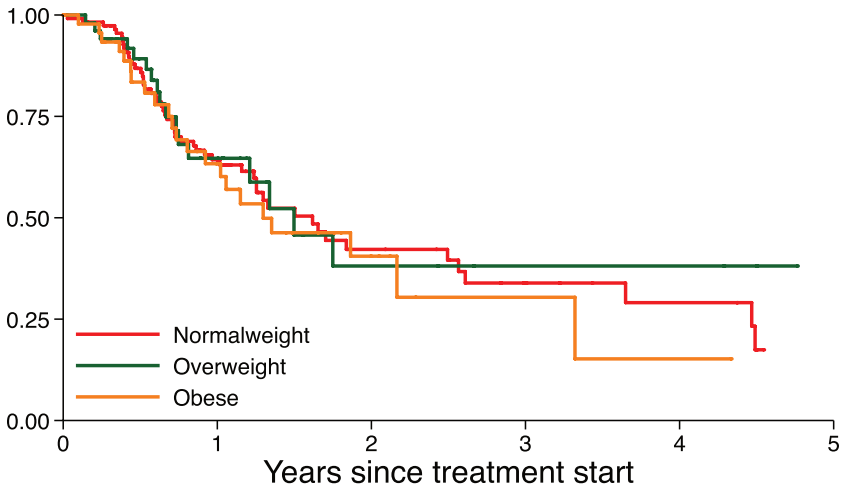

FIGURE 2. Proportion of patients without loss of response in 210 IBD patients treated with anti-TNF-α agents at 1 Danish center, according to BMI categories.[1] (1) Only 4 patients were treated for more than 4.5 years without experiencing an LOR; for these 4 patients, we censored the plot at 4.5 years after treatment initiation to avoid a disproportionate look of the graph.

TABLE 2: Hazard Ratios for Loss of Response in 210 Patients With IBD Treated With Anti-TNF-α Agents, According to BMI Categories

BMI category	Person-years[a]	Events[b]	Crude HR (95% CI)	Adjusted HR (95% CI)[c]	Adjusted HR (95% CI)[d]
All patients					
Normal weight	144	53	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Overweight	54	17	0.90 (0.52–1.55)	0.89 (0.51–1.56)	0.81 (0.45–1.44)
Obese	49	22	1.13 (0.69–1.87)	1.31 (0.76–2.24)	1.32 (0.76–2.30)
Crohn's disease					
Normal weight	91	38	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Overweight	30	12	0.94 (0.49–1.81)	0.95 (0.49–1.86)	0.73 (0.36–1.50)
Obese	29	8	0.59 (0.27–1.27)	0.58 (0.23–1.44)	0.56 (0.22–1.47)
Ulcerative colitis					
Normal weight	45	12	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Overweight	22	5	1.11 (0.39–3.15)	1.13 (0.32–3.93)	0.93 (0.24–3.64)
Obese	18	11	2.38 (1.05–5.42)	2.42 (1.03–5.70)	3.29 (1.31–8.31)
Infliximab					
Normal weight	112	42	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Overweight	43	17	1.09 (0.62–1.92)	1.19 (0.65–2.18)	1.24 (0.66–2.35)
Obese	39	20	1.32 (0.77–2.25)	1.56 (0.87–2.78)	1.75 (0.95–3.21)
Adalimumab					
Normal weight	32	11	1.00 (ref.)	1.00 (ref.)	-[e]
Overweight	11	0	-[e]	-[e]	-[e]
Obese	11	2	0.59 (0.12–2.78)	1.48 (0.03–83.38)	-[e]

[a]Person-years at risk, total per subgroup.
[b]Total events per subgroup.
[c]Adjusted for age, sex, and current smoking status.
[d]Adjusted for age, sex, current smoking status, IBD subtype, type of anti-TNF-α, concurrent medication, and former bowel resection.
[e]The small number of ADA patients could not bear the entire analysis, and the numbers listed should be considered with caution.

the physician who makes the decision of treatment intensification. Twelve percent of our patients were classified as primary nonresponders, and 43% experienced LOR, the first number being on the low end and the second on the high end of estimates from previously published studies.[29, 30] Inclusion of primary nonresponders in the main analysis did not alter the results noticeably.

A large portion of ADA patients were excluded due to missing data on BMI. Thus we were only able to include 30 patients treated with ADA; 4 of these were overweight, and 8 were obese. The results from the subgroup analysis of the ADA patients should therefore be considered with caution.

A secondary end point consisting solely of time to surgery after initiation of treatment showed no difference between BMI groups.

As the median follow-up of this study was <1 year, we were not able to report the long-term impact of obesity on treatment success.

Previous studies on the effect of obesity on IBD-related therapy have found obese IBD patients to be at higher risk of dose escalation in treatment with TNF-α agents[12–14]; in this study, we did not reproduce these results. We did not find consistent evidence suggesting that overweight patients should receive different treatment than the average normal weight patient, or that these patients should primarily be treated with weight-adjusted anti-TNF-α agents. However, in the subgroups of UC patients and patients treated with IFX, we saw a trend toward accelerated LOR with increasing BMI, but only in the small subgroup of obese UC patients did this association reach statistical significance. This could very well be a chance association, given the multiple statistical comparisons made in this study. That this subgroup should have an unusual response pattern was not a prespecified hypothesis and should be corroborated in other studies before any inferences can be made.

CONCLUSION

In this cohort of Danish IBD patients treated with anti-TNF-α agents, in which 86% of patients were treated with infliximab and 14% with adalimumab, we found no overall association between overweight/obesity and loss of response compared with normal weight patients with identical treatment regimens.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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REFERENCES

1. Hanauer SB, Feagan BG, Lichtenstein GR, et al; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359:1541–1549.
2. Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology*. 2004;126:402–413.
3. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353:2462–2476.
4. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006;130:323–333; quiz 591.
5. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132:52–65.
6. Ford AC, Sandborn WJ, Khan KJ, et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106:644–659, quiz 660.
7. González-Gay MA, González-Juanatey C. Rheumatoid arthritis: obesity impairs efficacy of anti-TNF therapy in patients with RA. *Nat Rev Rheumatol*. 2012;8:641–642.
8. Gremese E, Carletto A, Padovan M, et al; Gruppo Italiano di Studio sulle Early Arthritis (GISEA). Obesity and reduction of the response rate to anti-tumor necrosis factor α in rheumatoid arthritis: an approach to a personalized medicine. *Arthritis Care Res (Hoboken)*. 2013;65:94–100.
9. Klaasen R, Wijbrandts CA, Gerlag DM, et al. Body mass index and clinical response to infliximab in rheumatoid arthritis. *Arthritis Rheum*. 2011;63:359–364.
10. Gremese E, Bernardi S, Bonazza S, et al. Body weight, gender and response to TNF-α blockers in axial spondyloarthritis. *Rheumatology (Oxford)*. 2014;53:875–881.
11. Ottaviani S, Allanore Y, Tubach F, et al. Body mass index influences the response to infliximab in ankylosing spondylitis. *Arthritis Res Ther*. 2012;14:R115.
12. Bultman E, de Haar C, van Liere-Baron A, et al. Predictors of dose escalation of adalimumab in a prospective cohort of Crohn's disease patients. *Aliment Pharmacol Ther*. 2012;35:335–341.
13. Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2013;19:2118–2124.
14. Bhalme M, Sharma A, Keld R, et al. Does weight-adjusted anti-tumour necrosis factor treatment favour obese patients with Crohn's disease? *Eur J Gastroenterol Hepatol*. 2013;25:543–549.
15. Flores A, Burstein E, Cipher DJ, et al. Obesity in inflammatory bowel disease: a marker of less severe disease. *Dig Dis Sci*. 2015;60:2436–2445.
16. Seminerio JL, Koutroubakis IE, Ramos-Rivers C, et al. Impact of obesity on the management and clinical course of patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21:2857–2863.
17. Bilski J, Mazur-Bialy AI, Wierdak M, et al. The impact of physical activity and nutrition on inflammatory bowel disease: the potential role of cross talk between adipose tissue and skeletal muscle. *J Physiol Pharmacol*. 2013;64:143–155.
18. Blain A, Cattan S, Beaugerie L, et al. Crohn's disease clinical course and severity in obese patients. *Clin Nutr*. 2002;21:51–57.
19. Hu Q, Ren J, Li G, et al. The impact of obesity on the clinical course of inflammatory bowel disease: a meta-analysis. *Med Sci Monit*. 2017;23:2599–2606.
20. World Health Organization. Global Database on Body Mass Index. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed July 11, 2016.
21. Haens GR, D' Panaccione R, Higgins PDR, et al. The London position statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol*. 2011;106:199–212.
22. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006;55:749–753.
23. Hallas J, Hellfritzsch M, Rix M, et al. Odense pharmacoepidemiological database: a review of use and content. *Basic Clin Pharmacol Toxicol*. 2017;120:419–425.
24. Pedersen CB. The Danish civil registration system. *Scand J Public Health*. 2011;39:22–25.
25. Fasanmade AA, Adedokun OJ, Ford J, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol*. 2009;65:1211–1228.
26. Fasanmade AA, Adedokun OJ, Blank M, et al. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. *Clin Ther*. 2011;33:946–964.
27. Harper JW, Zisman TL. Interaction of obesity and inflammatory bowel disease. *World J Gastroenterol*. 2016;22:7868–7881.
28. Dotan I, Ron Y, Yanai H, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis*. 2014;20:2247–2259.
29. Caspersen S, Elkjaer M, Riis L, et al; Danish Crohn Colitis Database. Infliximab for inflammatory bowel disease in Denmark 1999-2005: clinical outcome and follow-up evaluation of malignancy and mortality. *Clin Gastroenterol Hepatol*. 2008;6:1212–1217; quiz 1176.
30. Ding NS, Hart A, De Cruz P. Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease - algorithm for practical management. *Aliment Pharmacol Ther*. 2016;43:30–51.