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Obesity and Response to Infliximab in Patients with Inflammatory Bowel Diseases: Pooled Analysis of Individual Participant Data from Clinical Trials

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Abstract

Aims: To assess whether obesity may affect response to infliximab, we conducted an individual participant data (IPD) pooled analysis using data from clinical trials of infliximab in inflammatory bowel diseases (IBD), using the Yale Open Data Access (YODA) Project.

Methods: We analysed IPD from 4 clinical trials of infliximab in adults with IBD (ACCENT-I, SONIC, ACT-1 and −2). Patients were categorized as obese (body mass index [BMI] ≥30kg/m^2) vs. non-obese, and by quartiles based on BMI or weight at time of trial entry. Primary outcome was clinical remission (Crohn's disease activity index [CDAI]<150 or pediatric CDAI<10, Mayo Clinic Score <3); secondary outcomes were clinical response and mucosal healing. Multivariable logistic regression analysis was performed, after adjusting for sex, smoking, disease activity, and concomitant prednisone and/or immunomodulators.

Results: We included 1207 infliximab-treated patients (mean age 37y, 51.6% males, 14% obese). Obesity was not associated with odds of achieving clinical remission (obese vs. non-obese: adjusted OR, 0.93 [95% CI, 0.47–1.46]; Q4 vs. Q1: aOR, 0.94 [0.61–1.47], p-value for

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trend=0.97), clinical response (Q4 vs. Q1: aOR, 0.84 [0.52–1.35], p=0.45) or mucosal healing (Q4 vs. Q1: aOR, 1.13 [0.55–2.34], p=0.95). These results were consistent across strata based on disease type (Crohn's disease and ulcerative colitis) and trial design (induction and maintenance therapy).

Conclusions: Based on IPD pooled analysis, obesity is not associated with inferior response to infliximab in patients with IBD. Future studies examining the association between obesity and fixed-dose therapies are warranted.

Keywords

Open science; posthoc analysis; obesity; complications; anti-TNF

INTRODUCTION

The global prevalence of obesity is rising, in parallel with the prevalence of inflammatory bowel diseases (IBD).(1) Approximately 15–40% of IBD patients are obese.(2–4) Obesity has been associated with increased risk of developing diseases such as Crohn's disease (CD) and rheumatoid arthritis (RA).(5) Among patients with IBD, obesity has been variably associated with more severe disease activity, inferior quality of life and higher burden of hospitalization.(6, 7) Observational studies in various rheumatic diseases have shown a negative impact of obesity on response to therapy, including tumor necrosis factor-α (TNF) antagonists, both agents that are dosed based on body weight (infliximab), as well as fixed-dosing regimens (adalimumab, golimumab, certolizumab pegol or etanercept),(8–11) though these results have inconsistent in patients with IBD.(12, 13) This may be attributed to low systemic drug exposure resulting in low trough concentrations in obese individuals (as has been observed in population pharmacokinetic studies), or may be attributed to obesity-induced low-grade inflammation, which can lead to higher systemic inflammatory burden.(4, 14, 15)

Less than 10% of clinical trials of anti-TNF agents have reported outcomes stratified by body mass index (BMI); where reported, inconsistent and dichotomous weight categories are used, and analyses are not adjusted for potential confounding variables, which limits a comprehensive assessment of impact of obesity on response to therapy.(11) Small, single-centre observational studies are frequently underpowered and use non-standardized outcome metrics; several have been published only in the abstract form. To overcome limitations of existing studies, and to comprehensively study the association between obesity and response to infliximab in patients with IBD, we conducted a pooled analysis of individual participant level data (IPD) from pivotal trials of infliximab in Crohn's disease (CD) and ulcerative colitis (UC), available through Yale Open Data Access (YODA) Project.(16)

METHODS

Data Source and Trials

Clinical trials of infliximab in adult patients with moderate to severe luminal CD or UC were accessed through the YODA project. This pioneering data-sharing model, started in 2011, housed at Yale University, provides access to de-identified IPD data, shared by data

holders, Johnson&Johnson, Medtronic, Inc. and SI-BONE, Inc.(16) A detailed research proposal was submitted by the investigators on October 2, 2015 (Protocol #2015–0612), and after review by the YODA scientific committee, was approved on October 20, 2015, with final data user agreements signed on December 9, 2015. Through this project, we were able to access trials of infliximab in IBD including: ACCENT-I (NCT00207662, Sponsor protocol No., C0168T21), ACCENT-II (NCT00207766, C0168T26) SONIC (NCT00094458, C0168T67), Targan et al (NCT00004941, C0168T20) ACT-1 (NCT00036439, C0168T37), ACT-2 (NCT00096655, C0168T46), UC-SUCCESS (NCT00537316, P04807), REACH (NCT00207675, C0168T47) and an open-label trial of infliximab in UC (NCT00336492, C0168T72). Of these, three trials with insufficient data on drug exposure or weight and outcome assessment (NCT00537316, NCT00004941, NCT00336492), one trial in patients with fistulising CD (NCT00207766) and one trial in pediatric patients (NCT00207675) were excluded.

From these trials, we created a cohort of infliximab-treated patients (with or without concomitant immunomodulators) to study the association between obesity and response to infliximab.

Exposure

We abstracted data on weight and height (where available) at time of trial entry (screening visit), to calculate body mass index (BMI). Patients within each trial were then divided into obese (BMI≥30kg/m^2) vs. non-obese (BMI<30kg/m^2), and quartiles by BMI (or weight where BMI measures were unavailable), which formed our primary exposure groups.

Outcome

Primary outcome of interest was achieving clinical remission. This was defined as: Crohn's disease activity index (CDAI <150) (in trials of adults with CD),(17) pediatric CDAI <10 (in pediatric trials of CD),(18) and Mayo Clinic Score [MCS] <3 (in trials of adults with UC).(19) Secondary outcomes of interest included: (a) clinical response (decrease in CDAI by >100 points [CR-100]; decrease in pediatric CDAI to 11–30 in children; decrease in MCS by ≥3 points and at least 30% from baseline), and (b) mucosal healing (in patients with CD, absence of ulceration in patients with ulcers present at baseline; MCS endoscopy sub-score of 0 or 1).

Outcomes were abstracted at primary endpoint of the included trials. Trials that reported outcomes for both induction therapy and maintenance were included in the analyses.

Confounding Variables

We also abstracted data on relevant confounding variables including: age, sex, smoking status (classified as never smokers, prior smokers classified as those who quit >1 year prior to trial entry and <1 year prior to trial entry, and current smokers), baseline disease activity (CD: severe >300, moderate 220–300, mild <220; UC: severe MCS>9, moderate 6–9, mild <6) and concomitant use of immunomodulators and/or prednisone.(17, 19) Results on disease duration, biochemical parameters including fecal calprotectin and albumin were inconsistently reported in trials, and hence, not included in the multivariate analysis.

Statistical Analysis

Baseline characteristics of trials participants were summarized as mean (standard deviation) or medians (range) for continuous variables, and as frequency (%) for categorical variables, and statistical differences in these characteristics by BMI/weight quartiles were assessed using ANOVA (with two sample t-tests for pairwise comparisons) for continuous variables and the chi-squared test for categorical variables. We compared proportions of patients with desirable outcome (clinical remission, response or mucosal healing) across quartiles of BMI/weight, across trials, using the chi-square test. Subsequently, we performed multivariable logistic regression analysis to analyze the association between obesity and outcomes, with study as a fixed covariate to account for inter-study differences and with and without adjusting for confounding variables (sex, smoking status, baseline disease activity, concomitant corticosteroids, concomitant immunomodulators). Age was also not reported in the YODA platform for ACT-1 and −2, and hence, was not included in multivariable analysis. Results were reported as odds ratio (OR) and 95% confidence intervals (CI), using Q1 (or non-obese status) as reference category. A p-value for the linear trend in odds across BMI/weight quartiles and BMI levels was estimated. Additionally, to evaluate dose-response relationship, we evaluated obesity as a continuous variable reporting risk of outcomes per 1 unit (1kg/m^2) increase in BMI and per 5kg increase in weight.

A priori subgroup analyses were performed based on disease type (CD and UC) and trial design (induction therapy [6–10 weeks] and maintenance trials [26–54 weeks]). All analyses were performed using R (the R Project for Statistical Computing).(20)

RESULTS

Patient Characteristics in Included Trials

In 4 trials (2 trials in patients with luminal CD, 2 trials in patients with UC), we included 1207 patients treated with infliximab. Table 1 lists the main characteristics of all patients, stratified by quartile of BMI or weight at entry to each trial. Median BMI of adult patients was 23.5 kg/m^2 (range, 13.0–49.2 kg/m^2). Of note, BMI was reported in two trials of CD, whereas only weight was reported in ACT trials in UC; hence, subgroup analyses were performed using quartiles of BMI (or weight where BMI was not reported). Approximately 32.1% patients were concomitantly on corticosteroids, and 46.0% were on immunomodulators. As compared to patients in the 1st quartile, patients in the 4th quartile of BMI/weight were older (Q4 vs. Q1: 41.0y vs. 32.0y, p<0.01), were more likely to be males (57.8% vs. 38.0%, p<0.01), had lower baseline disease activity (CDAI: 265 vs. 290, p<0.01; no difference in MCS), and were more likely to be on concomitant prednisone (40.2% vs. 27.7%, p<0.01) at time of cohort entry.

Obesity and Response to Infliximab

Clinical Remission: Obesity was not associated with the odds of achieving clinical remission. There was no significant difference in the proportion of infliximab-treated patients achieving clinical remission based on obesity status (obese vs. non-obese: 54.4% vs. 55.0%; OR, 0.92 [95% CI, 0.58–1.47], p=0.73) or by quartile analysis based on baseline BMI or weight (Q4 vs. Q1 – 49.1% vs. 47.6%; OR, 1.01 [0.71–1.45], p-value for linear

trend=0.75). Results were unchanged after adjusting for key covariates (aOR, 0.94 [0.60–1.47], p=0.97) (Figure 1, Table 2, eTable 1). When examining obesity as a continuous variable, there was no association between BMI (per 1 kg/m^2 increase in BMI: aOR, 0.99 [0.96–1.03]) (eTable 2) or weight (per 5kg increase in weight: aOR, 1.00 [0.94–1.05) and achievement of clinical remission (eTable 3). On analysis of each trial separately, obesity was associated with lower risk of achieving clinical remission only in ACT-2 (aOR, 0.25 [0.08–0.77], p=0.04) (eTables 4–7).

Clinical Response and Mucosal Healing: Obesity was not associated with risk of achieving clinical response or mucosal healing. After adjusting for covariates, infliximab-treated patients in the highest quartile of BMI were no less likely to achieve clinical response (aOR, 0.90 [0.55–1.49], p=0.66) or mucosal healing (aOR, 1.13 [0.55–2.34], p=0.95) (Figure 1, Table 2, eTable 1). Overall results were similar on analysis of BMI and weight as continuous variables (eTable 2 and 3), and across individual trials (eTables 4–7).

Subgroup Analysis

IBD type: Overall results were comparable on analyses stratified by disease type. Obesity was not significantly associated with risk of achieving clinical remission in infliximab-treated patients with CD (Q4 vs. Q1: aOR, 0.97 [0.56–1.68], p=0.87) or UC (aOR, 0.86 [0.38–1.92], p=0.98); of note, trials of UC only reported weight and not BMI (Table 3). Similar results were observed for outcomes of clinical response and mucosal healing, and on per unit analysis (eTable 2 and 3).

Trial design: In trials of induction therapy, there was no difference in risk of achieving clinical remission (aOR, 1.34 [0.83–2.16], p-value for linear trend=0.07), clinical response or mucosal healing based on baseline BMI or weight (Table 4). In trials of maintenance therapy, obesity was not associated with risk of achieving clinical remission in infliximab-treated patients (aOR, 0.92 [0.56–1.51], p=0.37) (Table 4).

DISCUSSION

In this pooled analyses of pivotal clinical trials of infliximab in 1207 patients with IBD, we observed that obesity does not significantly modify response to infliximab. These results were stable in patients with CD and UC, and in trials of induction and maintenance therapy. These findings suggest that in patients with IBD treated with an intravenous anti-TNF agent administered in a weight-based dosing regimen, obesity may not significantly influence short- to medium-term clinical outcomes. We are unable to comment on the potential impact of obesity on other biologic agents that are administered in a fixed dose, regardless of body weight.

Prior small observational studies in patients with IBD have shown conflicting results on how obesity may impact response to anti-TNF therapy. In a single-center, retrospective cohort study, Bhalme *et al* observed, in adalimumab-treated, but not in infliximab-treated patients, higher likelihood of dose escalation in obese patients than in non-obese (BMI >35kg/m^2 vs. BMI <25kg/m^2: 40% vs. 20%).(12) In contrast, in another retrospective cohort study of 124 patients with IBD, obese patients treated with infliximab were 3–9 times more likely to have

an IBD flare and require biologic dose escalation than normal weight.(13) Each unit increase in BMI was associated a 6% higher likelihood of CD flare (HR, 1.06; 95% CI, 1.02–1.11), and 30% higher likelihood of UC flare (HR, 1.30; 95% CI, 1.07–1.58). However, these uncontrolled observational studies used non-standard outcome measures and were unable to adequately control for potential confounding variables. Moreover, in real-world studies, it is probable that obese patients treated with infliximab may not receive optimal weight-appropriate therapy. Seminerio and colleagues observed that the average dose of infliximab in patients with class III obesity was ~4mg/kg, compared to 7.9mg/kg in normal BMI and 6.4 mg/kg body weight in overweight patients.(7) By using a more robust study design, including individual participant level data from clinical trials, with validated disease-specific outcomes, adequate drug exposure and adjusting for key confounding variables, we were able to demonstrate that obesity may not be an important effect modifiers in infliximab treated patients with IBD.

In contrast to IBD, data from prospective cohort studies in rheumatic diseases have more consistently suggested that obesity may negatively impact outcomes in infliximab-treated patients. In a prospective cohort of 89 patients with rheumatoid arthritis treated with infliximab, obese patients had lower rates of clinical response (measured using Disease Activity Score in 28 joints) as compared to non-obese patients, even after adjustment for baseline disease activity and anti-citrullinated protein antibody status (BMI>30kg/m^2 vs. 20–30kg/m^2 vs. <20kg/m^2: 50% vs. 75% vs. 84%).(10) Similarly, in 155 infliximab-treated patients with ankylosing spondylitis, Ottaviani and colleagues observed that only 26.5% of obese patients achieved clinical response, as compared to 77.6% normal BMI and 48.9% overweight patients.(21) These differences may be related to differences in pathogenesis, drug dosing and impact of severe disease in patients with IBD and rheumatic diseases. It is likely that in IBD patients, local mesenteric fat plays a more important role than systemic obesity, in contrast to other rheumatic diseases.(22) Dose of infliximab approved in patients with IBD is higher than that for other rheumatic diseases, which may overcome potentially detrimental effects of obesity. Finally, differential effect of confounding by disease severity in IBD and rheumatic diseases may also explain this finding – severe IBD is likely to result in weight loss and misclassification of obesity, whereas, severe rheumatic diseases would likely impact physical activity, promote sedentary lifestyle and contribute to obesity.

There are several limitations inherent to our study. First, though we pooled IPD data from trials, there were intrinsic differences in trial participants which may not have been adequately accounted for despite adjustment. However, our analyses were stable on multiple subgroup and sensitivity analyses, and also on analysis if each trial in isolation. Second, some trials reported only weight and hence, we were unable to consistently categorize exposure based on World Health Organization categories of obesity. Third, we were unable to study impact of obesity on trough concentrations of infliximab or need for dose escalation, and hence, we are unable to comment whether obesity may influence systemic drug exposure and clearance in infliximab-treated patients. Since most trials were limited to 1 year, long-term impact of obesity potentially mediated by sub-optimal drug concentrations cannot be ascertained. Fourth, data on weight was collected at time of cohort entry; hence, patients with recent weight changes prior to trial entry could not be ascertained which may have resulted in misclassification of some patients. However, since trials do not enroll very

sick patients who may have excessive amount of weight loss, the likely impact of such misclassification is low.

In conclusion, obesity does not significantly influence response to infliximab in patients with IBD, based on a pooled analysis of IPD from clinical trials. It is unknown whether obesity may influence response to fixed-dose therapies in patients with IBD. Post-hoc analyses of RCTs with individual participant level data are warranted to ascertain this association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STUDY HIGHLIGHTS

What is Current Knowledge?

- Obesity is associated with increased risk of developing inflammatory bowel disease, and may negatively impact natural history of disease
- Population pharmacokinetic studies suggest that obesity promotes biologic drug clearance
- Studies in patients with rheumatic diseases suggest that obese patients may have inferior response to infliximab and other biologic agents. However, it is unclear whether this holds true in patients with inflammatory bowel diseases

What this study adds?

- Based on individual participant data from 4 pivotal trials of infliximab in IBD with 1207 patients, we observed no association between obesity and response to infliximab after adjusting for relevant confounders
- These results were stable in trials of induction and maintenance therapy, and in patients with ulcerative colitis and Crohn's disease

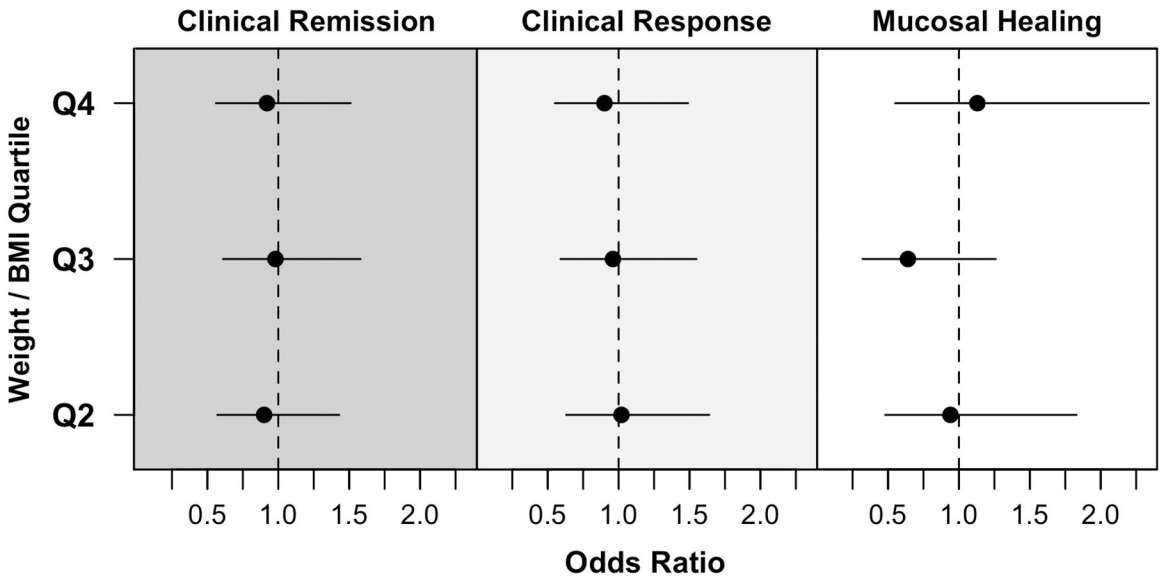

Figure 1.

Clinical remission, clinical response and mucosal healing in infliximab-treated patients across quartiles of BMI/weight, as compared to quartile 1 as reference.

Table 1.

Baseline characteristics of patients with inflammatory bowel diseases receiving infliximab in included clinical trials

Characteristics	All (n= 1207)	Q1 (n=305)	Q2 (n=297)	Q3 (n=307)	Q4 (n=296)
Age, mean (SD)	36.7 (12.2)	32.0 (11.1)	34.4 (11.1)	39.7 (12.6)	41.0 (11.6)
Sex: Female	584 (48.4%)	189 (62.0%)	156 (52.5%)	113 (36.8%)	125 (42.2%)
Male	623 (51.6%)	116 (38.0%)	141 (47.5%)	194 (63.2%)	171 (57.8%)
BMI (in kg/m^2), median range	23.5 (13.0, 49.2)	19.2 (13.0, 20.8)	22.2 (20.7, 23.6)	25.2 (23.5, 27.5)	30.8 (27.3, 49.2)
Smoking					
• Current	318 (26.3%)	88 (28.8%)	79 (26.6%)	77 (25.1%)	73 (24.7%)
• Past (Unknown)	231 (19.1%)	44 (14.4%)	49 (16.5%)	66 (21.5%)	72 (24.3%)
• Remote past	88 (7.2%)	9 (2.9%)	22 (7.4%)	28 (9.1%)	29 (9.8%)
• Recent past (<1y)	29 (2.4%)	7 (2.3%)	11 (3.7%)	7 (2.3%)	4 (1.4%)
• Never	541 (44.8%)	157 (51.4%)	136 (45.8%)	129 (42.0%)	118 (39.9%)
Disease type					
• Crohn’s disease	723 (60.0%)	187 (61.3%)	177 (59.6%)	186 (60.6%)	171 (57.8%)
• Ulcerative Colitis	484 (40.0%)	118 (38.7%)	120 (40.4%)	121 (39.4%)	125 (42.3%)
Disease activity					
• CDAI, mean (SD) for patients with CD	279.6 (58.9)	289.6 (53.5)	282.0 (55.4)	280.1 (63.4)	264.7 (60.4)
• Mayo Clinic Score, median (IQR)	8 (2)	9 (1.75)	9 (2)	8 (2)	8 (2)
Co-interventions					
• Prednisone	386 (32.1%)	84 (27.7%)	90 (30.5%)	92 (30.0%)	119 (40.2%)
• Immunomodulators					
◦ Azathioprine	383 (31.8%)	100 (33.0%)	93 (31.5%)	92 (30.0%)	98 (33.1%)
◦ 6-mercaptopurine	60 (6.9%)	13 (5.9%)	15 (7.0%)	17 (7.8%)	15 (7.1%)
◦ Methotrexate	28 (7.3%)	9 (8.8%)	8 (8.4%)	7 (7.3%)	4 (4.7%)

Table 2.

Rates of clinical remission, response and mucosal healing in infliximab-treated patients with IBD, by baseline BMI/weight quartile [variables adjusted for: sex, smoking status, baseline disease activity, concomitant corticosteroids, concomitant immunomodulators]

Outcome	Q1	Q2	Q3	Q4	p-trend
Clinical Remission					
• Proportion (n/N)	117 / 246 (47.6%)	107 / 234 (45.7%)	121 / 253 (47.8%)	109 / 241 (45.2%)	
• Unadjusted OR (95% CI)	1.0	0.99 (0.67, 1.45)	0.99 (0.68, 1.44)	0.95 (0.65, 1.39)	0.811
• Adjusted OR (95% CI)	1.0	0.90 (0.57, 1.43)	0.98 (0.61, 1.58)	0.92 (0.56, 1.51)	0.848
Clinical Response					
• Proportion (n/N)	155 / 247 (62.8%)	147 / 237 (62.0%)	158 / 255 (62.0%)	148 / 245 (60.4%)	
• Unadjusted OR (95% CI)	1.0	0.99 (0.68, 1.45)	0.94 (0.65, 1.36)	0.88 (0.60, 1.27)	0.453
• Adjusted OR (95% CI)	1.0	1.02 (0.63, 1.64)	0.96 (0.59, 1.55)	0.90 (0.55, 1.49)	0.660
Mucosal Healing					
• Proportion (n/N)	111 / 184 (60.3%)	103 / 180 (57.2%)	113 / 183 (61.7%)	109 / 180 (60.6%)	
• Unadjusted OR (95% CI)	1.0	0.89 (0.58, 1.36)	1.09 (0.71, 1.67)	1.06 (0.70, 1.63)	0.573
• Adjusted OR (95% CI)	1.0	0.94 (0.48, 1.83)	0.64 (0.32, 1.26)	1.13 (0.55, 2.34)	0.950

Table 3.

Subgroup analysis by IBD type.

Rates of clinical remission, response and mucosal healing in infliximab-treated patients with CD and UC, by baseline BMI/weight quartile [variables adjusted for: sex, smoking status, baseline disease activity, concomitant corticosteroids, concomitant immunomodulators]

Outcome	Q1	Q2	Q3	Q4	p-trend
CROHN'S DISEASE					
Clinical Remission					
• Proportion (n/N)	93 / 172 (54.1%)	88 / 157 (56.1%)	92 / 174 (52.9%)	86 / 151 (56.9%)	
• Unadjusted OR (95% CI)	1.0	1.10 (0.70, 1.72)	0.92 (0.59, 1.42)	1.10 (0.70, 1.72)	0.921
• Adjusted OR (95% CI)	1.0	1.03 (0.62, 1.73)	0.97 (0.58, 1.62)	0.97 (0.56, 1.68)	0.870
Clinical Response					
• Proportion (n/N)	110 / 172 (64.0%)	99 / 157 (63.1%)	101 / 174 (58.0%)	90 / 151 (59.6%)	
• Unadjusted OR (95% CI)	1.0	0.97 (0.61, 1.54)	0.74 (0.47, 1.16)	0.80 (0.50, 1.27)	0.193
• Adjusted OR (95% CI)	1.0	1.02 (0.61, 1.73)	0.86 (0.51, 1.44)	0.99 (0.57, 1.72)	0.797
Mucosal Healing					
• Proportion (n/N)	45 / 66 (68.2%)	45 / 60 (75.0%)	39 / 62 (62.9%)	38 / 55 (69.1%)	
• Unadjusted OR (95% CI)	1.0	1.40 (0.65, 3.12)	0.83 (0.39, 1.73)	1.12 (0.51, 2.46)	0.883
• Adjusted OR (95% CI)	1.0	1.86 (0.58, 6.33)	0.57 (0.19, 1.62)	1.02 (0.31, 3.39)	0.511
ULCERATIVE COLITIS					
Clinical remission					
• Proportion (n/N)	24 / 74 (32.4%)	19 / 77 (24.7%)	29 / 79 (36.7%)	23 / 90 (25.6%)	
• Unadjusted OR (95% CI)	1.0	0.74 (0.35, 1.55)	1.21 (0.60, 2.44)	0.69 (0.34, 1.40)	0.552
• Adjusted OR (95% CI)	1.0	0.75 (0.33, 1.64)	1.38 (0.61, 3.11)	0.86 (0.38, 1.92)	0.982
Clinical Response					
• Proportion (n/N)	45 / 75 (60.0%)	48 / 80 (60.0%)	57 / 81 (70.4%)	58 / 94 (61.7%)	
• Unadjusted OR (95% CI)	1.0	1.07 (0.55, 2.05)	1.59 (0.82, 3.15)	1.08 (0.57, 2.03)	0.601
• Adjusted OR (95% CI)	1.0	1.41 (0.68, 2.93)	2.46 (1.12, 5.51)	1.49 (0.71, 3.17)	0.246
Mucosal Healing					
• Proportion (n/N)	66 / 118 (55.9%)	58 / 120 (48.3%)	74 / 121 (61.2%)	71 / 128 (56.8%)	
• Unadjusted OR (95% CI)	1.0	0.74 (0.44, 1.23)	1.24 (0.74, 2.08)	1.04 (0.62, 1.72)	0.443
• Adjusted OR (95% CI)	1.0	0.73 (0.43, 1.23)	1.25 (0.71, 2.20)	1.10 (0.63, 1.93)	0.367

Table 4.

Subgroup analysis, by trials design.

Rates of clinical remission, response and mucosal healing in infliximab-treated patients in trials of induction therapy and maintenance therapy, by baseline BMI/weight quartile [variables adjusted for: sex, smoking status, baseline disease activity, concomitant corticosteroids, concomitant immunomodulators]

Outcome	Q1	Q2	Q3	Q4	p-trend
INDUCTION PHASE (Range 6–10 weeks)					
Clinical remission					
• Proportion (n/N)	111 / 273 (40.7%)	119 / 267 (44.6%)	132 / 285 (46.3%)	132 / 273 (48.4%)	
• Unadjusted OR (95% CI)	1.0	1.25 (0.87, 1.80)	1.32 (0.93, 1.88)	1.52 (1.06, 2.18)	0.024*
• Adjusted OR (95% CI)	1.0	1.41 (0.89, 2.23)	1.33 (0.84, 2.10)	1.34 (0.83, 2.16)	0.072
Clinical Response					
• Proportion (n/N)	176 / 273 (64.5%)	174 / 267 (65.2%)	192 / 284 (67.6%)	179 / 273 (65.6%)	
• Unadjusted OR (95% CI)	1.0	1.05 (0.73, 1.50)	1.14 (0.80, 1.62)	1.03 (0.73, 1.48)	0.748
• Adjusted OR (95% CI)	1.0	1.10 (0.76, 1.60)	1.28 (0.88, 1.86)	1.21 (0.83, 1.76)	0.243
Mucosal Healing					
• Proportion (n/N)	75 / 135 (55.6%)	76 / 133 (57.1%)	84 / 129 (65.1%)	73 / 131 (55.7%)	
• Unadjusted OR (95% CI)	1.0	1.06 (0.65, 1.72)	1.46 (0.89, 2.41)	0.98 (0.60, 1.60)	0.751
• Adjusted OR (95% CI)	1.0	1.10 (0.52, 2.31)	1.01 (0.44, 2.30)	0.69 (0.31, 1.55)	0.373
MAINTENANCE PHASE (Range 26–54 weeks)					
Clinical remission					
• Proportion (n/N)	117 / 246 (47.6%)	107 / 234 (45.7%)	121 / 253 (47.8%)	109 / 241 (45.2%)	
• Unadjusted OR (95% CI)	1.0	0.99 (0.67, 1.45)	0.99 (0.68, 1.44)	0.95 (0.65, 1.39)	0.811
• Adjusted OR (95% CI)	1.0	0.90 (0.57, 1.43)	0.98 (0.61, 1.58)	0.92 (0.56, 1.51)	0.848
Clinical Response					
• Proportion (n/N)	155 / 247 (62.8%)	147 / 237 (62.0%)	158 / 255 (62.0%)	148 / 245 (60.4%)	
• Unadjusted OR (95% CI)	1.0	0.99 (0.68, 1.45)	0.94 (0.65, 1.36)	0.88 (0.60, 1.27)	0.453
• Adjusted OR (95% CI)	1.0	1.02 (0.63, 1.64)	0.96 (0.59, 1.55)	0.90 (0.55, 1.49)	0.660
Mucosal Healing					
• Proportion (n/N)	111 / 184 (60.3%)	103 / 180 (57.2%)	113 / 183 (61.7%)	109 / 180 (60.6%)	
• Unadjusted OR (95% CI)	1.0	0.89 (0.58, 1.36)	1.09 (0.71, 1.67)	1.06 (0.70, 1.63)	0.573
• Adjusted OR (95% CI)	1.0	0.94 (0.48, 1.83)	0.64 (0.32, 1.26)	1.13 (0.55, 2.34)	0.950