Treatment failure of TNF-α inhibitors in obese patients with inflammatory bowel disease

- A cohort study.

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ABSTRACT

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 to 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 reference, while adjusting for confounders.

Results

Of 210 eligible patients, 92 (44%) experienced LOR. 180 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 to the normal weight group: overweight 0.89 (CI95% 0.51-1.56) and obese 1.31 (CI95% 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 (CI95% 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.
KEYWORDS:

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 1990’s has revolutionized the management of inflammatory bowel disease (IBD). Unfortunately, 13-40% of IBD patients are primary non-responders 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 - e.g. infliximab (IFX) - and for agents where dosing is fixed, e.g. 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 to normal weight patients.
**Materials and METHODS**

This is an observational cohort study of adult IBD patients treated with anti TNF-α agents at Department of Medical Gastroenterology, Odense University Hospital, Denmark in the period 01-01-2003 to 31-12-2015.

Patients were classified according to BMI: underweight (BMI < 18.5), normal weight (BMI 18.5 – 25), overweight (BMI 25 – 30) and obese (BMI > 30). We compared time to LOR between these groups.

Patients were included if they were at least 18 years old 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 primary non-responder to anti TNF-α therapy, and patients who discontinued treatment during or immediately after induction for other reasons. We defined primary non-response as: stop of treatment due to lack of effect within 16 weeks after the first treatment.

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 (i.e. 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, behavior and activity of the disease, following the Montreal classification.

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. Linkage of the data was performed using the personal identification number which is a unique identifier assigned to all Danish individuals. 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 non-satisfactory 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. 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 one of the events mentioned above. Using Cox regression, we calculated hazard ratios for the three BMI categories: normal weight, overweight and obese, with the normal weight group as 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 is not required according to Danish law.
RESULTS

We identified a cohort of 374 patients. 44 patients (12%) were excluded due to primary non-response to treatment. In 57 patients (15%) treatment was discontinued during, - or just after completing induction treatment for reasons other than non-response. 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. 18 patients were excluded due to BMI < 18.5.

210 patients were eligible for analysis (figure 1), with a median follow up of 9.6 months (interquartile range: 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, ADA 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%) of 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 (CI95%: 0.52-1.55) and 1.13 (CI95%: 0.69-1.87) compared with the normal weight category. Thus none of the BMI categories showed a statistically significant higher hazard ratio of LOR, compared with the normal weight category.

Figure 2 shows the Kaplan Meier plot of the four 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 (CI95%: 1.05-5.42) (Table 2).

We redid the subgroup analyses and included phenotype and severity for Crohn’s Disease and ulcerative colitis respectively. This did not produce any discernible change of the results.

The IFX subgroup showed a trend towards 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 non-responders. 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, supplemental digital content)

Also, we established a secondary endpoint 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 (0.49-2.11) for overweight and 1.04 (0.50-2.16) for obese patients, compared with the normal weight group.

Lastly we evaluated the association between anti-TNF 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 (CI95%: 0.97-1.04) for all IBD patients, 0.97 (CI95%: 0.93-1.02) for CD patients, and 1.08 (CI95%: 1.00-1.17)
for UC patients. After adjustment for possible confounders the UC patients had a hazard ratio of 1.11 (CI95%: 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, i.e. 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.\textsuperscript{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 in order 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 composition, i.e. 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, i.e. increased dose or decreased time between treatments, as a proxy marker for LOR. Dose escalation was based on a clinical assessment of whether or not 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 the physician who makes the decision of treatment intensification.

12% of our patients were classified as primary non-responders and 43% experienced LOR, the first
number being in the low end and the second in the high end of estimates from previous published studies.\textsuperscript{29,30} Inclusion of primary non-responders 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 endpoint consisting solely of time to surgery after initiation of treatment showed no difference between BMI-groups.

Since the median follow-up of this study was < 1 year, we were not able to report 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-\(\alpha\) agents,\textsuperscript{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-\(\alpha\) agents. However, in the subgroups of UC patients and patients treated with IFX we saw a trend towards 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 pre-specified 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-\(\alpha\) agents we found no overall association
between overweight/obesity and loss of response compared with normal weight patients with identical treatment regimen.
Acknowledgements

Anne Berg (Nurse, Department of Medical Gastroenterology) is acknowledged for assistance with establishing the cohort.

Conflicts of interest

The authors declare no conflicts of interest.

Authors’ contributions

All authors contributed to the conception and design of the study, and the interpretation of the data. Kenneth Grønkjær Madsen and Jens Kjeldsen acquired the data. Kenneth Grønkjær Madsen drafted the manuscript. All authors revised the manuscript critically for important intellectual content. All authors approved the final version for submission.
References


12. Bultman E, Haar C de, Liere-Baron A van, et al. Predictors of dose escalation of


Figure Legends

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

Figure 2
Proportion of patient without loss of response in 210 IBD patients treated with anti TNF-α agents at one Danish center, according to BMI categories.¹

Footnote below figure 2:
¹) Only 4 patients were treated for more than 4.5 years without experiencing a LOR, for these 4 patients we censored the plot at 4.5 years after treatment initiation to avoid a disproportionate look of the graph.

List of Supplemental Digital Content

1, Table 3, format: word table.
Figure 1

Adult patients treated with anti TNF-agents due to IBD at Odense University Hospital
n = 374

Primary non-response: n = 44
Non TNF-naïve: n = 3
Induction treatment only / not completed: n = 57
Weight or height not available: n = 37
No info on primary response: n = 4
BMI < 18.5: n = 18
Treated with other agent than ADA or IFX: n = 1

Included in analysis
n = 210

Normal weight
BMI 18.5 - 24.9
n = 114

Overweight
BMI 25 - 29.9
n = 51

Obese
BMI ≥ 30
n = 45
Figure 2

Years since treatment start

- Normalweight
- Overweight
- Obese
Table 1 Characteristics of 210 adult IBD patients treated with anti TNF-α agents. Divided in subgroups by BMI category.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 210)</th>
<th>Normal weight (n = 114 (54%))</th>
<th>Overweight (n = 51 (24%))</th>
<th>Obese (n = 45 (21%))</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age1, median (IQR, years)</td>
<td>32 (24-44)</td>
<td>29 (23-43)</td>
<td>35 (27-44)</td>
<td>35 (29-45)</td>
<td>0.22</td>
</tr>
<tr>
<td>Years since diagnosis1, median (IQR)</td>
<td>3 (0-8)</td>
<td>4 (0-10)</td>
<td>3 (1-8)</td>
<td>3 (1-8)</td>
<td>0.34</td>
</tr>
<tr>
<td>Male sex</td>
<td>80 (38.1%)</td>
<td>41 (36.0%)</td>
<td>22 (43.1%)</td>
<td>17 (37.8%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Current smoker</td>
<td>63 (30.0%)</td>
<td>41 (36.0%)</td>
<td>13 (25.5%)</td>
<td>9 (20.0%)</td>
<td>0.10</td>
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<tr>
<td>Anti TNF-α agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>180 (85.7%)</td>
<td>96 (84.2%)</td>
<td>47 (92.2%)</td>
<td>37 (82.2%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>30 (14.3%)</td>
<td>18 (15.8%)</td>
<td>4 (7.8%)</td>
<td>8 (17.8%)</td>
<td>0.30</td>
</tr>
<tr>
<td>IBD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>127 (60.5%)</td>
<td>72 (63.2%)</td>
<td>30 (58.8%)</td>
<td>25 (55.6%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>74 (35.2%)</td>
<td>38 (33.3%)</td>
<td>19 (37.3%)</td>
<td>17 (37.8%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Unclassified IBD</td>
<td>9 (4.3%)</td>
<td>4 (3.5%)</td>
<td>2 (3.9%)</td>
<td>3 (6.7%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Concurrent drug use2</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-ASA3</td>
<td>71 (33.8%)</td>
<td>34 (29.8%)</td>
<td>20 (39.2%)</td>
<td>17 (37.8%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Immunosuppressant</td>
<td>91 (43.3%)</td>
<td>50 (43.9%)</td>
<td>18 (35.3%)</td>
<td>23 (51.1%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Systemic steroid</td>
<td>97 (46.2%)</td>
<td>48 (42.1%)</td>
<td>30 (58.8%)</td>
<td>19 (42.2%)</td>
<td>0.12</td>
</tr>
<tr>
<td>CD, location</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileitis</td>
<td>26 (20.5%)</td>
<td>14 (19.4%)</td>
<td>5 (16.7%)</td>
<td>7 (28.0%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Colitis</td>
<td>34 (26.8%)</td>
<td>20 (27.8%)</td>
<td>7 (23.3%)</td>
<td>7 (28.0%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Ileocolitis</td>
<td>67 (52.8%)</td>
<td>38 (52.8%)</td>
<td>18 (60.0%)</td>
<td>11 (44.0%)</td>
<td>0.48</td>
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<td>CD, Behaviour</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Luminal</td>
<td>80 (63.0%)</td>
<td>40 (55.6%)</td>
<td>23 (76.7%)</td>
<td>17 (68.0%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Strictureing</td>
<td>27 (21.3%)</td>
<td>19 (26.4%)</td>
<td>4 (13.3%)</td>
<td>4 (16.0%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Fistulising</td>
<td>20 (15.7%)</td>
<td>13 (18.1%)</td>
<td>3 (10.0%)</td>
<td>4 (16.0%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>22 (17.3%)</td>
<td>14 (19.4%)</td>
<td>4 (13.3%)</td>
<td>4 (16.0%)</td>
<td>0.76</td>
</tr>
<tr>
<td>UC, location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcerative proctitis</td>
<td>11 (14.9%)</td>
<td>4 (10.5%)</td>
<td>5 (26.3%)</td>
<td>2 (11.8%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>40 (54.1%)</td>
<td>22 (57.9%)</td>
<td>8 (42.1%)</td>
<td>10 (58.8%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>23 (31.1%)</td>
<td>12 (31.6%)</td>
<td>6 (31.6%)</td>
<td>5 (29.4%)</td>
<td>0.96</td>
</tr>
<tr>
<td>UC, severity</td>
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</tr>
<tr>
<td>Chronic active</td>
<td>64 (86.5%)</td>
<td>34 (89.5%)</td>
<td>16 (84.2%)</td>
<td>14 (82.4%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Acute severe</td>
<td>10 (13.5%)</td>
<td>4 (10.5%)</td>
<td>3 (15.8%)</td>
<td>3 (17.6%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Prior bowel resection</td>
<td>35 (16.7%)</td>
<td>19 (16.7%)</td>
<td>9 (17.6%)</td>
<td>7 (15.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Prior fistula surgery/drainage</td>
<td>20 (9.5%)</td>
<td>12 (10.5%)</td>
<td>4 (7.8%)</td>
<td>4 (8.9%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Loss of response</td>
<td>92 (43.8%)</td>
<td>53 (46.5%)</td>
<td>17 (33.3%)</td>
<td>22 (48.9%)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Abbreviations: IBD Inflammatory Bowel Disease. CD Crohn’s Disease. UC Ulcerative Colitis. TNF-α Tumour Necrosis Factor-α.

1) Age at start of anti TNF-α treatment
2) We defined concurrent medication as having retrieved a prescription within the last 3 months before initiation of anti
TNF-α treatment.
3) ATC code: A07EC
4) ATC code: L04AX01 or L04AX03
5) ATC code: H02AB
Table 2

Hazard ratios (HR) for loss of response in 210 patients with IBD treated with anti TNF-α agents, according to BMI categories.

<table>
<thead>
<tr>
<th>BMI category</th>
<th>Personyears¹</th>
<th>Events²</th>
<th>CrudeHR³</th>
<th>AdjustedHR⁴</th>
<th>AdjustedHR⁵</th>
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<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight</td>
<td>144</td>
<td>53</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
</tr>
<tr>
<td>Overweight</td>
<td>54</td>
<td>17</td>
<td>0.90 (0.52-1.55)</td>
<td>0.89 (0.51-1.56)</td>
<td>0.81 (0.45-1.44)</td>
</tr>
<tr>
<td>Obese</td>
<td>49</td>
<td>22</td>
<td>1.13 (0.69-1.87)</td>
<td>1.31 (0.76-2.24)</td>
<td>1.32 (0.76-2.30)</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Normal weight</td>
<td>91</td>
<td>38</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
</tr>
<tr>
<td>Overweight</td>
<td>30</td>
<td>12</td>
<td>0.94 (0.49-1.81)</td>
<td>0.95 (0.49-1.86)</td>
<td>0.73 (0.36-1.50)</td>
</tr>
<tr>
<td>Obese</td>
<td>29</td>
<td>8</td>
<td>0.59 (0.27-1.27)</td>
<td>0.58 (0.23-1.44)</td>
<td>0.56 (0.22-1.47)</td>
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<td>Ulcerative Colitis</td>
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<tr>
<td>Normal weight</td>
<td>45</td>
<td>12</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
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<tr>
<td>Overweight</td>
<td>22</td>
<td>5</td>
<td>1.11 (0.39-3.15)</td>
<td>1.13 (0.32-3.93)</td>
<td>0.93 (0.24-3.64)</td>
</tr>
<tr>
<td>Obese</td>
<td>18</td>
<td>11</td>
<td>2.38 (1.05-5.42)</td>
<td>2.42 (1.03-5.70)</td>
<td>3.29 (1.31-8.31)</td>
</tr>
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<td>Infliximab</td>
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</tr>
<tr>
<td>Normal weight</td>
<td>112</td>
<td>42</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
</tr>
<tr>
<td>Overweight</td>
<td>43</td>
<td>17</td>
<td>1.09 (0.62-1.92)</td>
<td>1.19 (0.65-2.18)</td>
<td>1.24 (0.66-2.35)</td>
</tr>
<tr>
<td>Obese</td>
<td>39</td>
<td>20</td>
<td>1.32 (0.77-2.25)</td>
<td>1.56 (0.87-2.78)</td>
<td>1.75 (0.95-3.21)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Normal weight</td>
<td>32</td>
<td>11</td>
<td>1.00 (Ref.)</td>
<td>1.00 (Ref.)</td>
<td>- (Ref)</td>
</tr>
<tr>
<td>Overweight</td>
<td>11</td>
<td>0</td>
<td>- (Ref)</td>
<td>- (Ref)</td>
<td>- (Ref)</td>
</tr>
<tr>
<td>Obese</td>
<td>11</td>
<td>2</td>
<td>0.59 (0.12-2.78)</td>
<td>1.48 (0.03-83,38)</td>
<td>- (Ref)</td>
</tr>
</tbody>
</table>

Abbreviations: TNF-α Tumour Necrosis Factor-α

1) Person-years at risk, total per sub-group.
2) Total events per sub-group.
3) 95% confidence interval in parenthesis.
4) Adjusted for: age, sex and current smoking status. 95% confidence interval in parenthesis.
5) Adjusted for: age, sex, current smoking status, IBD-subtype, type of anti TNF-α, concurrent medication, and former bowel resection. 95% confidence interval in parenthesis.
6) The small number of ADA patients could not bear the entire analysis, and the numbers listed should be considered with caution.