Serum Concentration of Anti-TNF Antibodies, Adverse Effects and Quality of Life in Patients with Inflammatory Bowel Disease in Remission on Maintenance Treatment

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Abstract

Background and aims: High serum concentrations of infliximab [IFX] and adalimumab [ADA] may be associated with adverse effects in patients with inflammatory bowel disease [IBD]. We aimed to investigate whether high anti-tumour necrosis factor [TNF] trough levels [TLs] were associated with toxicity and impaired quality of life [QoL].

Methods: We conducted a prospective cohort study in IBD patients in clinical and biochemical remission on IFX or ADA maintenance therapy. Trough serum concentrations and antidrug antibodies were measured in addition to biochemical markers of inflammation in serum and stool to confirm quiescent disease. QoL was assessed using the Inflammatory Bowel Disease Questionnaire and 36-item short form. Side effects such as fatigue and arthralgia were measured with a visual analogue score [VAS]. Skin toxicity was reported with a European Organization for Research and Treatment of Cancer-derived score.

Results: In all, 252 IBD patients on maintenance anti-TNF therapy were screened, of whom 95 [73 with Crohn's disease, 22 with ulcerative colitis; 72 on IFX, 23 on ADA] were in clinical and biochemical remission and were included. Median TLs were 5.5 µg/ml and 6.6 µg/ml for IFX and ADA, respectively. Patients with anti-TNF TLs above median had lower IBDQ scores than patients with lower TLs [IBDQ 176 vs 187, p = 0.02], particularly regarding systemic symptoms and emotional status. A trend towards lower SF-36 and higher fatigue scores was observed in the higher anti-TNF TL group. Skin and arthralgia scores were not significantly different between the groups.

Conclusions: IBD patients with higher anti-TNF serum concentrations had significantly lower disease-specific QoL. Fatigue, arthralgia, and skin lesions do not occur more often in these patients. These data are reassuring that high serum concentrations of anti-TNF antibodies are not toxic.

Keywords: Anti-TNF; inflammatory bowel disease; quality of life; side effects; trough levels
1. Introduction

The introduction of anti-tumour necrosis factor [TNF] agents, such as infliximab [IFX] and adalimumab [ADA], has led to major progress in the treatment of inflammatory bowel disease [IBD]. IFX and ADA are effective to induce and maintain remission in patients with Crohn’s disease [CD] and ulcerative colitis [UC].

Detectable IFX or ADA trough levels [TLs] are associated with higher rates of sustained clinical and biochemical remission and improved endoscopic outcomes. Moreover, IFX TL > 3 μg/ml at the start of maintenance treatment has been predictive for sustained response to IFX, and patients receiving maintenance treatment with ADA were less likely to discontinue therapy if TLs were higher than 5.6 μg/ml at week 12. Recently, a prospective trial compared therapeutic drug monitoring [TDM]-based IFX dosing with conventional dosing in IBD patients, suggesting a therapeutic window for IFX TLs between 3 and 7 μg/ml.

Chronic use of anti-TNF agents has been associated with a range of side effects, such as dermatological manifestations, arthralgia, infusion or injection side reactions, infections, or malignancies. A proportion of patients with IBD or rheumatoid arthritis receiving treatment with anti-TNF agents experience paradoxical inflammatory, mainly psoriatic arthritis or eczema-like, skin lesions. The aetiological mechanism which is responsible for this phenomenon has not been completely clarified. It is hypothesised that, in predisposed individuals, TNF inhibition can cause a cytokine unbalance, resulting in local upregulation of plasmacytoid dendritic cells that unrestrictedly produce interferon-α, and abundance of IL-23, thereby inducing the onset of psoriatic skin lesions. Topical therapy with corticosteroids resolves these symptoms in some patients, whereas other patients are forced to discontinue the anti-TNF treatment, but can effectively switch to an alternative anti-TNF agent. Typically, these symptoms subside after discontinuation of the drug.

Furthermore, arthralgia has been associated with maintenance treatment with anti-TNF agents in IBD patients with quiescent disease. Elevated antinuclear antibodies [ANA] and anti-dsDNA levels are detectable in these patients. Similarly, paradoxical polyarthritis flares have been observed in rheumatoid arthritis patients treated with IFX maintenance therapy. A dose increase of IFX resulted in further deterioration of arthritis complaints in these patients.

Clinical observations suggest that higher TLs, eg above the arbitrary level of 7 μg/ml for IFX, may be associated with side effects. Distinguishing these potential drug-related side effects from extra-intestinal manifestations can be challenging, since skin lesion and arthritis can also occur as an extra-intestinal manifestation in IBD patients.

Sparse data exist about the possible correlation between high anti-TNF TLs and suspected anti-TNF side effects. Therefore, we aimed to investigate anti-TNF TLs, quality of life and side effects in IBD patients who are in clinical and biochemical remission receiving maintenance therapy with IFX or ADA.

2. Methods

2.1. Study design

This prospective study was performed at two centres in Amsterdam, The Netherlands [an academic referral centre, the Academic Medical Centre and a regional teaching hospital, Onze Lieve Vrouwe Gasthuis], between January, 2013 and March, 2015. Patients with a confirmed diagnosis of IBD, receiving IFX or ADA maintenance therapy, were eligible for screening. Clinical remission was assessed with the Harvey Bradshaw Index [HBI] and Simple Clinical Colitis Activity Index [SCCAI] for CD and UC, respectively, using cut-off values of < 5 points for both scores.

Biochemical remission was defined as faecal calprotectin concentrations < 230 μg/g and C-reactive protein [CRP] serum levels ≤ 5 mg/l.

Serum concentrations of IFX and ADA were measured at trough [immediately before an infusion or injection] along with anti-IFX and anti-ADA antibodies, using a radio-immunoassay. Biochemical parameters known to be associated with fatigue or ongoing inflammation were also measured including haemoglobin [Hb], haematocrit, leukocyte and thrombocyte count, serum albumin, serum vitamin D, and thyroid stimulating hormone [TSH].

Patients who were found to have antidrug antibodies, hypothyroidism or anaemia [defined by WHO criteria as < 13.0 g/dl for men and < 12.0 g/dl for women] were excluded. In addition, patients with established rheumatic [rheumatoid arthritis, ankylosing spondylitis], or dermatological [psoriasis, eczema] diseases, or documented rheumatic or dermatological symptoms before initiating anti-TNF agents, and patients with significant and established comorbidity [including cancer, infectious diseases, irritable bowel syndrome, etc], or pregnancy were also excluded.

2.2. Outcomes measures

IFX and ADA serum TLs were assessed using an enzyme-linked immune sorbent assay [ELISA] and disease-related quality of life [DRQL] reflecting their symptoms in the 8 weeks before the current infusion or injection.

HRQL was measured with the validated Medical Outcomes Study 36-item Short Form [SF-36] which has a Physical and a Mental component score [PCS an MCS] across 36 items. A higher score indicates a better HRQL. This questionnaire has been used for comparing HRQL of IBD patients with the general population.

Disease-related quality of life [DRQL] was measured using the IBDQ [Inflammatory Bowel Disease Questionnaire], a 32-item questionnaire consisting of four dimensions: bowel-related symptoms [eg loose stools, abdominal pain], systemic function [eg fatigue, sleep pattern], social function [eg ability to attend work and social events], and emotional status [eg anger, depression, irritability]. The response for each question ranges from 1 to 7 [1 corresponding to ‘significant impairment’ and 7 to ‘no impairment’]. The overall IBDQ score is the sum of the responses to each of the IBDQ questions. The total IBDQ ranges from 32 [very poor DRQL] to 224 [perfect DRQL].

Patients in symptomatic remission usually have a score of 170 or more. The validity, reliability, and responsiveness of this questionnaire has been previously established.

Patients were asked to complete questionnaires consisting of several items on health-related quality of life [HRQL] and disease-related quality of life [DRQL] reflecting their symptoms in the 8 weeks before the current infusion or injection.

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Patients were asked to rate fatigue and arthralgia using 100-mm visual analogue scores [VAS]. VAS scales are frequently used in HRQL analyses as a reliable instrument to measure pain and have been validated in several studies. Patients were presented a line scale indicating ‘no fatigue’ and ‘no arthralgia’ [far left] to ‘extreme fatigue’ and ‘extreme arthralgia’ [far right]. The indicated value on this continuum led to a number between 0 and 100mm, with greater scores indicating greater pain/fatigue severity and intensity.
In addition, fatigue was also assessed using the FACIT-F [Functional Assessment of Chronic Illness Therapy-Fatigue] scale. This instrument consists of 13 items, each of which is scored on a 5-point Likert scale of fatigue symptoms, with lower scores reflecting more severe fatigue.\textsuperscript{18,19}

Finally, three questions specifically focusing on dermatological side effects of anti-TNF agents were selected from European Organization for Research and Treatment of Cancer [EORTC] questionnaires. A skin score was composed consisting of questions about rash, xerosis, and pruritus. Each question could be answered from 1 [no symptoms at all] to 4 [severe symptoms], resulting in a summed score from 3–12, with higher scores indicating more severe skin lesions.

2.3. Statistical analysis and ethical considerations
Data are presented as median with interquartile range [IQR] in case of non-parametric data and as mean with standard deviation in case of parametric data. Due to different pharmacokinetics of IFX and ADA [intravenous vs subcutaneous administration] and presumable different therapeutic ranges, subgroup analysis for treatment characteristics and median/interquartile analysis for IFX or ADA TLs were performed separately. The two study cohorts were divided in halves based on anti-TNF TL outcomes, resulting in two groups; lower than or equal to median TL [H1] or higher than the 50th percentile [H2]. The lower or upper halves of IFX and ADA were combined for analysis. Data were non-parametric distributed and analysed comparing medians with the Mann-Whitney U test or Fisher’s exact test. Except for anti-TNF TLs, questionnaire outcomes were also compared based on patient (gender, body mass index [BMI], smoking), disease [diagnosis, duration] or treatment [type of anti-TNF, duration, combination therapy] factors. A $p$-value $< 0.05$ was considered statistically significant. Correlations were analysed using Spearman’s rank correlation coefficient. Data were analysed using SPSS\textsuperscript{®} 20.0 [IBM Corp., Armonk, NY, USA].

This study was approved by the local ethical committee according to national Dutch legislation. All patients informed consent to participate in this study. Patients receiving IFX were investigated during their infusion clinic visit in parallel with clinical care. Patients receiving ADA were assessed during an extra hospital visit on the day before or on the day of the next ADA injection to ensure that trough concentrations were measured.

3. Results
3.1. Patient and treatment characteristics.
A total of 252 patients were found to be eligible based on clinical disease activity and were invited to participate; 188 consented to participate and were enrolled in this study. At time of infusion or injection, six patients appeared to have [previously unknown] comorbidity or clinical activity and were excluded. Incomplete laboratory results or questionnaires resulted in the exclusion of eight additional patients. After review of the biochemical results, 73 [60 CD, 13 UC] of the remaining 173 [42\%] patients that were in clinical remission appeared not to be in biochemical remission [ie faecal calprotectin level $> 250 \mu g/g$ and/or CRP $> 5$ mg/l]. Median [IQR] faecal calprotectin levels in the group with elevated faecal calprotectin values were 588 [370–1279] \mu g/g. Five of the 173 [3\%] patients had detectable antidrug antibodies [three to IFX, two to ADA with antidrug antibody titres ranging from 16 to 140 AU/ml]. These patients were excluded from further analysis, resulting in a final study cohort of 95 patients [Figure 1] who were truly in remission.
Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Total [n = 95]</th>
<th>H1 [n = 51] IFX ≤ 5 µg/ml ADA ≤ 6.6 µg/ml</th>
<th>H2 [n = 44] IFX &gt; 5 µg/ml ADA &gt; 6.6 µg/ml</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease, n [%]</td>
<td>73 [77%]</td>
<td>37 [73%]</td>
<td>36 [82%]</td>
<td>ns</td>
</tr>
<tr>
<td>Montreol age A1, A2, A3 [n]</td>
<td>10, 56, 7</td>
<td>6, 25, 6</td>
<td>4, 31, 1</td>
<td>ns</td>
</tr>
<tr>
<td>Montreol location L1, L2, L3 [n]</td>
<td>12, 17, 44</td>
<td>8, 7, 22</td>
<td>4, 10, 22</td>
<td>ns</td>
</tr>
<tr>
<td>Montreol behaviour B1, B2, B3 [n]</td>
<td>26, 21, 26</td>
<td>13,12,12</td>
<td>13, 10, 13</td>
<td>ns</td>
</tr>
<tr>
<td>Perianal disease [n]</td>
<td>22</td>
<td>9</td>
<td>13</td>
<td>ns</td>
</tr>
<tr>
<td>Ulcerative colitis, n [%]</td>
<td>22 [23%]</td>
<td>14 [28%]</td>
<td>8 [18%]</td>
<td></td>
</tr>
<tr>
<td>Montreol extent: E1, E2, E3 [n]</td>
<td>1, 14, 7</td>
<td>1, 8, 5</td>
<td>0, 6, 2</td>
<td></td>
</tr>
<tr>
<td>Age [years], median [IQR]</td>
<td>42 [32–52]</td>
<td>46</td>
<td>40</td>
<td>0.10</td>
</tr>
<tr>
<td>Gender (female), n [%]</td>
<td>57 [58%]</td>
<td>30 [59%]</td>
<td>25 [57%]</td>
<td>ns</td>
</tr>
<tr>
<td>Body mass index [kg/m²]</td>
<td>24 [22.1–25.5]</td>
<td>24.1</td>
<td>23.2</td>
<td>ns</td>
</tr>
<tr>
<td>Current smoking, n [%]</td>
<td>24 [25%]</td>
<td>14 [28%]</td>
<td>10 [23%]</td>
<td>ns</td>
</tr>
<tr>
<td>Disease duration [years], median [IQR]</td>
<td>12 [7–21]</td>
<td>13</td>
<td>12</td>
<td>ns</td>
</tr>
<tr>
<td>BMI, median [IQR]</td>
<td>1 [0–2]</td>
<td>1</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td>SCCAI, median [IQR]</td>
<td>0 [0–1]</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Haematocrit [%]</td>
<td>40 [0.39–0.44]</td>
<td>0.41</td>
<td>0.42</td>
<td>ns</td>
</tr>
<tr>
<td>Leukocyte count [*10⁹], median [IQR]</td>
<td>7.1 [5.6–8.9]</td>
<td>6.9</td>
<td>7.6</td>
<td>0.21</td>
</tr>
<tr>
<td>Thrombocytes [*10¹²], median [IQR]</td>
<td>262 [209–308]</td>
<td>271</td>
<td>258</td>
<td>ns</td>
</tr>
<tr>
<td>Albumin [g/l], median [IQR]</td>
<td>44 [42–47]</td>
<td>44</td>
<td>45</td>
<td>ns</td>
</tr>
<tr>
<td>C-reactive protein [mg/l], median [IQR]</td>
<td>1.0 [0.5–2.6]</td>
<td>1.0</td>
<td>1.0</td>
<td>ns</td>
</tr>
<tr>
<td>Vitamin D [nmol/l], median [IQR]</td>
<td>62 [48–79]</td>
<td>61</td>
<td>62</td>
<td>ns</td>
</tr>
<tr>
<td>Faecal calprotectin [µg/g], median [IQR]</td>
<td>65 [20–124]</td>
<td>68</td>
<td>54</td>
<td>ns</td>
</tr>
</tbody>
</table>

H1, lower half; H2, upper half; IFX, infliximab; ADA, adalimumab; IQR, interquartile range; HBI, Harvey Bradshaw Index; SCCAI, Simple Clinical Colitis Activity Index; ns, not significant.

Table 2. Anti-TNF characteristics.

<table>
<thead>
<tr>
<th>Anti-TNF characteristics</th>
<th>Infliximab [n = 72]</th>
<th>Adalimumab [n = 23]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose and frequency, n [%]</td>
<td>5 mg/kg, q8wk: 55 [76%]</td>
<td>40 mg, q2wk: 21 [91%]</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg, q6wk: 8 [11%]</td>
<td>40 mg, q1wk: 2 [9%]</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg, q4wk: 4 [6%]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg/kg, q8wk: 2 [3%]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg/kg, q6wk: 2 [3%]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg/kg, q4wk: 1 [1%]</td>
<td></td>
</tr>
<tr>
<td>Treatment duration [years], median [IQR]</td>
<td>4 [2–8]</td>
<td>2 [1–4]</td>
</tr>
<tr>
<td>Combination therapy, n [%]</td>
<td>23 [32%]</td>
<td>5 [22%]</td>
</tr>
<tr>
<td>Serum concentration [µg/ml], median [IQR]</td>
<td>5.0 [3.0–7.0]</td>
<td>6.6 [5.5–9.0]</td>
</tr>
</tbody>
</table>

TNF, tumour necrosis factor; IQR, interquartile range; q ... wk, once every ... weeks.

[76/95 = 80%] of patients received regular IFX (5 mg/kg, once every 8 weeks [q8wk]) or ADA [40 mg, q2wk] maintenance therapy with a median treatment duration of 4 and 2 years, respectively. Concomitant immunomodulators were used by 32% of the patients on IFX and 22% of those on ADA.

3.2. Classification according lower/upper anti-TL halves

Because of different pharmacokinetic profiles [due to intravenous vs subcutaneous administration] patients were divided into groups for lower and upper halves of median serum anti-TNF TLs for both anti-TNF agents. The median [IQR] IFX TL was 5.0 [3.0–7.0] µg/ml and median ADA TL 6.6 [5.5–9.9] µg/ml. Patients with median or lower than median anti-TNF TLs were classified as lower half anti-TNF TL group [H1], whereas patients with higher than median anti-TNF TLs were classified as upper half anti-TNF TL group [H2].

Patient characteristics were comparable between the H1 and H2 groups, and biochemical parameters that are known to be associated with fatigue or active inflammation [eg Hb, CRP, faecal calprotectin] were not significantly different between the two study groups [Table 1].

3.3. Generic and disease-related quality of life

The median IBDQ of all patients was 181 [Table 3]. The IBDQ was significantly lower in patients with higher anti-TNF TLs [176 vs 187, p = 0.02] [Figure 2]. Patients with higher anti-TNF TLs scored significantly lower on two particular domains of IBDQ: systemic symptoms [4.8 vs 5.0, p = 0.03] and emotional status [5.46 vs 5.83, p = 0.04] [Figure 3A]. Overall, anti-TNF TLs were inversely correlated with IBDQ, but this did not reach significance [r = -0.15, p = 0.14].

A trend towards a lower physical and mental component summary scale of SF-36 was observed in the H2 group compared with patients in the H1 group [Table 3]. These patients scored lower or equally at each separate aspect of the SF-36 compared with patients with lower anti-TNF TLs [Figure 3B].
Table 3. Side effects outcomes according to anti-TNF TL lower/upper halves.

<table>
<thead>
<tr>
<th>Side effects outcomes</th>
<th>H1 [n = 51]</th>
<th>H2 [n = 44]</th>
<th>p-Value</th>
<th>Total [n = 95]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36: PCS</td>
<td>50 [43–54]</td>
<td>48 [38–53]</td>
<td>0.21</td>
<td>49 [41–54]</td>
</tr>
<tr>
<td>VAS arthralgia [mm]</td>
<td>8 [0–21]</td>
<td>16 [1–45]</td>
<td>0.15</td>
<td>10 [0–27]</td>
</tr>
</tbody>
</table>

Lower IBDQ indicates impaired quality of life. In contrast, lower VAS scores indicate less symptoms.

TFN, tumour necrosis factor; TL, trough level; H1, lower half; H2, upper half; IQR, interquartile range; IBDQ, Inflammatory Bowel Disease Questionnaire; SF-36, Short form-36; PCS: Physical Component Summary; MCS, Mental Component Summary; VAS, visual analogue scale, FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue.

Figure 2. IBDQ (median) according to anti-TNF TL halves. IBDQ, Inflammatory Bowel Disease Questionnaire; TFN, tumour necrosis factor; IFX, infliximab; ADA, adalimumab; TL, trough level.

3.4. Side effects

Skin score, VAS arthralgia, and fatigue or FACIT-F were not significantly different in the H1 group compared with H2 (Table 3).

3.5. Patient, disease or treatment factors associated with quality of life and side effects

Subgroup analysis had its limitations due to smaller patient samples. Analysis by patient, disease, or treatment-related factors revealed impaired disease-specific quality of life in CD patients compared with UC patients [IBDQ: 178 vs 193, $p = 0.04$] as well as in current smokers vs non-smoking patients [169 vs 186, $p = 0.02$] (Table 4). This difference was independent of the anti-TNF TLs in these groups. No differences were found with respect to IBDQ between patients receiving IFX compared with ADA maintenance treatment or combination therapy [with thiopurines] vs anti-TNF monotherapy. After exclusion of patients receiving higher than standard doses [ie IFX: $> 5$ mg/kg q8wk or ADA: $> 40$ mg q2wk], patients with high TLs [H2, $n = 32$], had a median IBQ score of 165 vs 190 [$p < 0.0001$] for patients on standard maintenance therapy with low TLs [H1, $n = 44$].

Furthermore, smokers had a lower mental component score for the SF-36 and a trends towards more arthralgia. Visual analogue scale scores for fatigue were higher in patients with CD compared with UC [46 vs 24 mm, $p = 0.05$], in female patients [52 vs 31 mm, $p = 0.06$], and in patients on combination therapy [55 vs 32 mm, $p = 0.07$].

4. Discussion

In this study we show that IBD patients with quiescent disease receiving maintenance treatment with IFX or ADA have an impaired disease-specific quality of life in the presence of relatively higher serum concentrations of anti-TNF antibodies.

Individualised therapy based on TDM has shown to improve treatment outcomes and has important economic consequences in patients with IBD. In addition, TDM might also result in a reduction in side effects caused by anti-TNF agents. Minimisation of side effects of IFX and ADA maintenance treatment remains a relevant and challenging issue in the management of IBD patients. The clinical observation that patients sometimes develop fatigue, joint pain, and skin problems despite ‘deep’ clinical and biochemical remission prompted us to perform the current study.

Quality of life of patients in our cohort is comparable to previous studies in which IBD patients were studied receiving anti-TNF maintenance therapy and with quiescent disease. Differences in IBDQ were particularly found in systemic symptoms and emotional status. Furthermore, trends were observed towards lower generic quality of life in patients with higher anti-TNF serum concentrations. A change of 3–5 points in the MCS or PCS scale is generally considered to be a clinically meaningful change. Although most patients exhibit a generally high level of generic and disease-specific quality of life corresponding with inactive disease, our study suggests that dose reduction may improve quality of life in these patients.

Interestingly, during screening we found that a large proportion of [mainly CD] patients who were in clinical remission had elevated biochemical inflammatory markers. This is in line with previous findings, such as the post hoc analysis of the SONIC trial, that clinical disease activity poorly correlates with biochemical and mucosal disease activity in CD patients. Although remission was not evaluated by endoscopy, we used strict cut-offs for both CRP and calprotectin levels in present study. Faecal calprotectin has previously demonstrated to serve as a reliable surrogate marker for endoscopic disease activity in both CD and UC.
Available data with regard to IFX TLs and side effects are conflicting. In a study by Huang et al., median IFX TLs were significantly higher in patients who reported dermatological adverse effects, and females reported more adverse effects [skin rashes, arthralgia, neuropathy, and infusion reactions] than males. In the present study, a trend was observed towards a lower quality life and more fatigue in female patients. On the other hand, Protic and colleagues did not observe a statistical significant difference in serum IFX concentrations in the group of patients with anti-TNFinduced psoriasis compared with controls. In addition, in a large retrospective cohort study from Leuven, drug levels did not play a role in developing skin-related adverse events in IBD patients treated with anti-TNF agents. Other work revealed a higher number of skin lesions in patients who received anti-TNF monotherapy compared with patients who were treated with combination therapy consisting of anti-TNF agents and thiopurines. Our study did not find an association with skin lesions as reported by the patients themselves. This might be explained by the fact that our cohort consisted of an unselected cohort of patients suffering from relatively few skin lesions.

A limitation of the present study is the relatively small number of patients. Hence, larger numbers of patients may be required to assess the background of fatigue, arthralgia, and skin lesions in IBD. Nonetheless, we were able to detect significant differences in quality of life in this prospectively well-documented cohort. To our knowledge, this study is one of the first to report about this challenging problem in IBD patients in association with anti-TNF TLs.

In clinical practice it remains challenging to differentiate between possible anti-TNF-related side effects and extra-intestinal manifestations that are often seen in IBD patients. We attempted to minimise this confounder in the present study by excluding patients with active clinical or biochemical disease. Therefore, it is unlikely for them to have IBD-associated extra-intestinal manifestations. A 2-year prospective cohort study from Finland reported that paediatric IBD patients with skin reactions had a low degree of intestinal inflammation based on their faecal calprotectin levels compared with patients without skin lesions. In line with this observation, a French cohort study of skin lesions in IBD patients treated with anti-TNF agents revealed that the disease was quiescent in the vast majority of patients. Moreover, assessing potential side effects of high anti-TNF serum concentrations in this subset of patients in clinical remission is of particular interest, since the anti-TNF dose might be de-escalated while retaining disease control. Dose reduction in these patients is also important from an economic point of view. Considering > 7 µg/ml for IFX and > 10 µg/ml for ADA as arbitrary ‘supratherapeutic’ cut-offs, 23% [22/95] of patients in our cohort had ‘supratherapeutic’ anti-TNF TLs, while being in clinical in biochemical remission. To date, the TAXIT study is the only trial in IBD patients in which anti-TNF therapy was de-escalated below a certain IFX serum concentration. Patients may even benefit from treatment de-escalation to a lower ‘therapeutic’ threshold of 3 µg/ml. Further trails are warranted to define the therapeutic window of anti-TNF TLs.

Skin lesions and arthralgia were reported in our study by the patients themselves, hence they were not objectified by experts such as dermatologists or rheumatologists. Therefore, it is not possible to identify the type of skin or joint complaints that are responsible for

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**Figure 3.** (A) IBDQ subdomains; (B) SF-36 subdomains. IBDQ, Inflammatory Bowel Disease Questionnaire; TL, trough level; SF-36, Short form-36.
impairing the quality of life in these patients. However, considering the rising interest in patient-reported outcomes, these observations could still serve as valuable outcomes of therapy and of vital importance in affecting quality of life in these patients. As opposed to previous studies, we report an unbiased cohort comprising both IBD patients with dermatological and/or articular symptoms and patients without such symptoms [serving as controls].

Patients were asked to score their skin and joint symptoms, fatigue, and quality of life over the past 8 weeks prior to the current infusion or injection. Some patients typically experience adverse symptoms in the first days after an anti-TNF administration, possibly related to immunological response mechanisms. Other patients develop symptoms in the days before the next administration, due to [subclinical] relapsing disease activity. We did not aim to make a distinction between these two phenomena, but excluded patients with circulating and measurable antibodies to anti-TNF agents and/or active clinical and biochemical disease activity.

The mechanisms behind an impaired quality of life in patient with high circulating anti-TNF levels remain uncertain. This cohort comprised patients receiving higher than standard maintenance anti-TNF dosing, thereby not excluding a reverse phenomenon, in which patients with decreased quality of life could have received ‘unwarranted’ dose escalation resulting in higher anti-TNF TLs. However subgroup analysis, with solely the patients receiving standard anti-TNF maintenance dosing, showed impaired disease-related quality of life in these patients with high anti-TNF TLs compared with patients with low TLs on standard maintenance therapy, indicating that this reverse phenomenon does not explain the impaired quality of life in these patients.

Various ‘paradoxical’ immunological mechanisms have been proposed, such as the deposition of immune complexes or cytokine shifts, to explain skin lesions in anti-TNF treated patients with IBD. IL-36y and IL-17C were found to be increased in CD patients with TNF antagonist-induced psoriasisiform skin lesions compared with healthy controls. Serum concentrations of IL-17A and IL-23 were significantly higher in CD patients who developed skin lesions under anti-TNF therapy, compared with patients without such lesions. Genetic susceptibility might also contribute to anti-TNF related psoriasis-like skin lesions. A recent study showed that patients carrying the IL23R gene are more likely to develop these skin lesions. The skin lesions were histologically characterised by infiltrates of IL-17A/IL-22-secreting Th17 cells, interferon [IFN]-γ-secreting Th1 lymphocytes, and IFN-α-expressing cells. All patients were successfully treated with the anti-p40-IL-12/IL-23 antibody ustekinumab. We did not aim to investigate the genetic background of these patients and this remains an interesting subject for future research.

In conclusion, higher anti-TNF TLs are associated with impaired quality of life in IBD patients who are in clinical and biochemical remission with IFX or ADA maintenance treatment. This finding may support de-escalating therapy in patients with ‘supertherapeutic’ anti-TNF TLs that are in clinical and biochemical remission. Future research could include a prospective evaluation with dermatological and rheumatological consultation as well as intensive blood sampling to unravel the immunological and genetic background that drive these paradoxical side effects of anti-TNF agents in patients with IBD.

Author Contributions
JF and LMV were equally involved in study concept and design, recruitment of patients, acquisition of data; analysis, and interpretation of data, drafting of the manuscript, and statistical analysis. JF, TS, CP, and GB were involved in recruitment of patients and critical revision of the manuscript for important intellectual content. GD and ML were involved in study concept and design, recruitment of patients, and critical revision of the manuscript for important intellectual content and supervision of the study.

Conflict of Interest
JF has received speaker’s fees from Takeda, MSD, and Abbvie. LMV has nothing to declare. JF has served as a speaker for MSD Abbott and has served as a consultant for Ferring Pharmaceuticals, Schering Plough, Abbvie, and Pfizer. TS has nothing to declare. CP has served as a speaker for Schering Plough, Falk Pharma, Tramedico, Abbott Inc., and Glaxo Smith Kline, and as a consultant for Schering Plough, Falk Pharma, Tramedico, Abbott Inc., and Glaxo Smith Kline, and has received research funding from Schering Plough, Falk Pharma, Tramedico, Abbott Inc., and Glaxo Smith Kline. GB has received

### Table 4. Predisposing factors.

<table>
<thead>
<tr>
<th>Predisposing factors</th>
<th>IBHQ</th>
<th>SF36 PCS</th>
<th>SF36 MCS</th>
<th>Skin score</th>
<th>VAS Arthralgia</th>
<th>VAS Fatigue</th>
<th>FACIT Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD vs UC [n = 73]</td>
<td>178 vs 193 $p = 0.04$ $p = 0.14$</td>
<td>$p = 0.17$</td>
<td>$p = 0.48$</td>
<td>$p = 0.73$</td>
<td>46 vs 24, $p = 0.05$</td>
<td>52 vs 31, $p = 0.06$</td>
<td>$p = 0.25$</td>
</tr>
<tr>
<td>Gender female [n = 55]</td>
<td>177 vs 188 $p = 0.06$</td>
<td>$p = 0.24$</td>
<td>$p = 0.56$</td>
<td>$p = 0.25$</td>
<td>52 vs 31, $p = 0.06$</td>
<td>52 vs 31, $p = 0.06$</td>
<td>$p = 0.17$</td>
</tr>
<tr>
<td>BMI &gt; 25 kg/m² [n = 29]</td>
<td>$p = 0.88$</td>
<td>$p = 0.96$</td>
<td>$p = 0.24$</td>
<td>$p = 0.11$</td>
<td>$p = 0.98$</td>
<td>$p = 0.63$</td>
<td></td>
</tr>
<tr>
<td>Smoking [n = 24]</td>
<td>169 vs 186 $p = 0.02$</td>
<td>$p = 0.04$</td>
<td>$p = 0.06$</td>
<td>17 vs 6 $p = 0.25$</td>
<td>$p = 0.16$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration &gt; 10 years [n = 54]</td>
<td>$p = 0.27$</td>
<td>$p = 0.40$</td>
<td>$p = 0.57$</td>
<td>$p = 0.43$</td>
<td>$p = 0.30$</td>
<td>$p = 0.30$</td>
<td></td>
</tr>
<tr>
<td>IFX [n = 72] vs ADA</td>
<td>$p = 0.97$</td>
<td>$p = 0.21$</td>
<td>$p = 0.15$</td>
<td>$p = 0.88$</td>
<td>$p = 0.17$</td>
<td>37 vs 43, $p = 0.06$</td>
<td></td>
</tr>
<tr>
<td>Treatment duration &lt; 2 years [n = 54]</td>
<td>$p = 0.80$</td>
<td>$p = 0.94$</td>
<td>$p = 0.68$</td>
<td>$p = 0.20$</td>
<td>$p = 0.96$</td>
<td>$p = 0.87$</td>
<td></td>
</tr>
<tr>
<td>Combination therapy [n = 28]</td>
<td>$p = 0.99$</td>
<td>$p = 0.92$</td>
<td>$p = 0.17$</td>
<td>$p = 0.27$</td>
<td>$p = 0.94$</td>
<td>55 vs 32, $p = 0.07$</td>
<td></td>
</tr>
</tbody>
</table>

Medians are given in bold for $p < 0.10$. Lower IBHQ indicates impaired quality of life. In contrast, lower VAS scores indicate less symptoms.

CD, Crohn’s disease; UC, ulcerative colitis; BMI, body mass index; IFX, infliximab; ADA, adalimumab; IBHQ, Inflammatory Bowel Disease Questionnaire; SF-36, Short form-36; PCS, Physical Component Summary; MCS, Mental Component Summary; VAS, visual analogue scale; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue.
consulting fees from Abbott Laboratories and lecture fees from Abbott Laboratories, Merck Sharp & Dohme, and Ferring Pharmaceuticals; e has received research grants from Abbott Laboratories, Crucell, and Ferring Pharmaceuticals. GD has served as a speaker for Abbott Inc., Tillotts, Tramedico, Ferring, MSD, UCB, Norgine, and Shire, and as a consultant for Abbott Laboratories, Actogenix, Centocor, Cosmo, Engene, Ferring Pharmaceuticals, GlaxoSmithKline, Jansen Biologics, Millenium Pharmaceuticals, MSD, Novonordisk, PDL Biopharma, Pfizer, SetPoint, Shire, Takeda, Teva, and UCB, and has received research funding from Abbott Inc., Jansen Biologics, Given Imaging, MSD, Dr Falk Pharma, and Photopill. ML has served as speaker and/or principal investigator for AbbVie, Coviden, Dr Falk, Ferring Pharmaceuticals, Merck Sharp & Dohme, Receptos, Takeda, and Tramedico. He has received research grants from AbbVie, Merck Sharp & Dohme, and Achmea healthcare.

References
43. Huang V, Dhami N, Fedorak DK, et al. 3 infliximab trough levels are correlated with infliximab-associated adverse events. Gastroenterology; 146:S1.