Higher Infliximab Levels Are Not Associated With an Increase in Adverse Events in Inflammatory Bowel Disease

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Background: Patients requiring optimization of therapy for suboptimal response and/or targeting more robust outcomes may eventually reach high serum levels. Data evaluating the relationship between infliximab concentration and toxicity are limited. The aim of this study was to evaluate the frequency of adverse events (AEs) in inflammatory bowel disease (IBD) patients with infliximab higher-range (HR) and lower-range (LR) trough levels.

Methods: We performed a retrospective analysis of 180 patients with at least 1 measurement of serum infliximab from 2012 to 2016. The cohort was divided according to an infliximab level cutoff of 15 µg/mL (HR and LR). The primary outcome was frequency of AEs, including infections, dermatological manifestations, and infusion reactions, between the 2 groups. The secondary outcomes included frequencies of all AEs (dermatological manifestations, infusion reactions, autoimmune reactions, and opportunistic and serious infections) in both groups. AEs were also compared against observed infliximab level quartiles using logistic regression analysis.

Results: A total of 53 AEs in 47 patients were reported in the overall cohort. In the LR group, there were 36 AEs recorded in 30 patients, whereas in the HR group, 17 AEs were experienced by 17 patients. Patients with HR levels did not have a higher prevalence of infections in comparison with patients with LR levels (12.2% vs 18.8%; $P = 0.3$). Stratification of infliximab levels by quartiles showed a comparable frequency of infection.

Conclusions: Our findings indicate that higher infliximab serum concentrations are not associated with a higher frequency of infections.

Key Words: adverse effect, infliximab, inflammatory bowel disease, level

INTRODUCTION

The clinical introduction of tumor necrosis factor (TNF) inhibitors has deeply revolutionized the treatment of inflammatory bowel disease (IBD). Anti-TNF therapy is effective for induction and maintenance therapy in Crohn's disease (CD) and ulcerative colitis (UC).[1, 2] Despite their widely demonstrated efficacy in the management of IBD, concerns about potential adverse events (AEs) remain an important issue for both health care providers and patients. Anti-TNF agents have been found to be associated with a range of AEs, the most common of which is infection.[3, 4]

Therapeutic drug monitoring is becoming a mainstay for optimal management of biologic therapy in patients with IBD.[5, 6] Evidence has accumulated demonstrating correlation between TNF antagonist serum concentrations and treatment outcomes, such as clinical remission and mucosal healing.[7, 8] Essentially, low or undetectable serum levels and the presence of antidrug antibodies (ADAs) are associated with worse outcomes. It has been suggested that an infliximab trough level between 3 and 7 µg/mL might be the optimal therapeutic window.[9] Evolving data point toward mucosal healing as the optimal therapeutic goal with the potential to alter the natural history of the disease.[10] Based on exposure-response studies of anti-TNF therapy and heterogeneity in clinical practice, achieving the desired clinical effect and ideally a more robust endoscopic end point may require treatment protocols with greater dosing than originally described in the registration trials.[11, 12] A potential outcome of such an approach may be that patients are exposed to higher drug levels. This underscores the importance of better understanding the relationship between serum drug concentrations and anti-TNF-related AEs. The aim of this study was to evaluate the safety of infliximab treatment among IBD patients with higher serum drug levels by comparing the frequency of AEs among various infliximab concentrations.

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METHODS

Patient Selection

Consecutive patients with IBD who were treated with infliximab at Mount Sinai Hospital (Toronto, Canada) between November 2012 and June 2016 were retrospectively evaluated. All patients with at least 1 infliximab trough level measurement using a homogenous mobility shift assay (Prometheus Laboratories, San Diego, CA, USA) were included. Patients who had less than 3 months of available clinical data around the time of the measurement or had insufficient clinical follow-up were excluded. The lower limits of quantification for detectable infliximab with this assay were 1.0 μg/mL and 3.1 U/mL for anti-infliximab antibodies (ATIs).[13] A therapeutic serum infliximab level was defined as greater than or equal to 3.0 μg/mL[6].

Data Collection and Definitions

Demographic and clinical data were retrieved through electronic medical records and reports regarding AEs sent to the referring doctors from drug company coordinators or infusion centers. All AEs including infection, dermatological manifestation, infusion reaction (IR), autoimmune disorder, cardiovascular complications, and malignancies during a 6-month period (3 months before and after the date of serum infliximab measurement) were documented. Drug discontinuation related to AEs was also recorded. A serious AE was defined as any life-threatening event resulting in hospitalization or leading to significant disability. Serious infections were defined in the same way. IR was categorized as either immediate or delayed and was divided according to severity.[14] Serious infusion reactions were those determined to be life-threatening or that resulted in significant disability or hospitalization.

Demographic and clinical characteristics collected included sex, age at infliximab serum measurement and IBD diagnosis, duration of infliximab treatment, disease location and phenotype according to the Montreal classification,[15] smoking history, prior and concurrent medication use, previous history of intestinal surgery, maintenance dosing regimen, reason for discontinuation of treatment if applicable, complete blood count, C-reactive protein (CRP; mg/L), and albumin (g/L) level.

Clinical and endoscopic disease status was assigned in proximity to the date of infliximab level assessment (within the 2 months before or after the date of level measurement) based on a physician's description and endoscopy results up to 2 months before or after the date of infliximab measurement. The study protocol was approved by the Mount Sinai Hospital Institutional Research Review Board.

Outcomes

The primary outcome was the proportion of infections in subjects with low-range (LR) vs high-range (HR) infliximab serum concentrations. The cut-point chosen was 15 μg/mL, which is significantly higher than the usual therapeutic upper trough limit of 7 mg/mL. This level was chosen to examine a more "extreme" cohort to enhance the possibility of detecting a safety signal should one exist at high infliximab serum concentrations. Secondary outcomes included frequencies of all AEs (dermatological manifestations, IRs, autoimmune reactions, and opportunistic and serious infections) in both groups. We also stratified infliximab levels by quartiles and compared with prevalence of infections in each group. Additional analysis was performed comparing proportions of infections in 3 subgroups divided by infliximab levels that are perhaps more representative of those seen in typical practice: (a) <8 μg/mL; (b) 8–20 μg/mL; and (c) >20 μg/mL.

Statistical Analysis

Continuous variables were expressed as the mean and standard deviation, and categorical variables as a percentage. The Mann-Whitney *U* test was used to compare continuous variables. Categorical variables were compared using the Fisher exact test. For the primary and secondary analysis, comparisons of adverse events between the subgroups according to all the different divisions were performed using the Fisher exact test. The proportion of any AEs was calculated by dividing the number of patients experiencing an adverse event by the number of patients in each group. AEs were also compared against observed infliximab (IFX) level quartiles using logistic regression analysis. Alternative models with covariates such as time on drug, sex, and IBD phenotype were also explored.

In addition, univariate logistic regression analysis was performed. Infection was the dependent variable, and the independent variables were sex, age, IBD subtype, smoking history, disease duration, disease activity, concomitant steroids or immunomodulators, infliximab levels, and ATI status. Multivariable logistic regression was performed to identify predictors between infection and variables found to be associated with infection on univariate analysis. A P value of <0.05 was considered statistically significant. Two-sided statistical tests were used for all analyses. Statistical analysis was completed using Medcalc software (Mariakerke, Belgium).

RESULTS

Patients

A total of 197 subjects met the original criteria for inclusion in the study. Seventeen of these patients were excluded due to lack of clinical follow-up (10) and due to insufficient clinical information (7) to document AEs. Patient characteristics are shown in Table 1. Age at inclusion, age at diagnosis, and disease duration were all significantly higher in the cohort with serum infliximab concentration below 15 ug/mL (31.5 vs 26 years, $P < 0.01$; 21 vs 17 years, $P < 0.01$; and 9.5 vs 7 years, $P = 0.01$;

TABLE 1: Characteristics of Patients With IFX Levels Lesser or Greater than 15 µg/ml

	IFX < 15 µg/mL (n = 90)	IFX > 15 µg/mL (n = 90)	*P*
Female, No. (%)	44 (49)	42 (51)	0.88
Age at serum draw, median (IQR), y	31.5 (40–22.25)	26 (30.75–21)	<0.01
Age at diagnosis, median (IQR), y	21 (29–15)	17 (23–13)	0.01
Disease duration, median (IQR), y	9.5 (13–5)	7 (11–4)	0.01
IBD subgroups, No. (%)			
CD	53 (58.8)	49 (54.4)	0.65
UC	30 (33.3)	33 (36.6)	0.75
IBDU	7 (7.7)	8 (8.8)	1
CD location (Montreal classification), No. (%)			
Ileal (L1)	15 (28.3)	12 (24.4)	0.65
Colonic (L2)	11 (20.7)	12 (24.4)	0.99
Ileo-colonic (L3)	27 (51)	25 (51)	0.84
Upper GI (L4)	17 (32)	12 (24.4)	0.38
Perianal, No. (%)	20 (37.7)	25 (51)	0.43
CD phenotype (Montreal classification), No. (%)			
Inflammatory (B1)	20 (37.7)	20 (40.8)	1
Stricturing (B2)	21 (39,6)	18 (36.7)	0.68
Penetrating (B3)	12 (22.6)	11 (22.4)	0.99
Prior surgery for CD, No. (%)	21 (39.6)	14 (28.5)	0.21
UC extent, No. (%)	30 (33.3)	33 (36.6)	
Distal colitis (E1)	2 (6.6)	2 (6)	1
Left-sided colitis (E2)	6 (20)	6 (18.1)	0.76
Pancolitis (E3)	22 (73.3)	25 (75.7)	0.53
Prior colectomy, No. (%)	1 (3.3)	1 (3)	1
Smoking status, No. (%)			
Nonsmoker	81 (90)	83 (92.2)	0.99
Current smoker	9 (10)	7 (7.8)	0.79
Previous immunomodulators, No. (%)	79 (88)	74 (82)	0.9
Previous anti-TNF, No. (%)	6 (7)	10 (11)	0.43
Concomitant immunosuppressant, No. (%)	21 (23.3)	32 (35.5)	0.1
Concomitant steroids, No. (%)	10 (11.1)	15 (16.6)	0.38
Disease status, No. (%)			
Clinical remission	29 (38.6)	60 (75)	<0.01
Endoscopic remission	20 (36.3)	26 (52)	0.11
Elevated CRP (>5 mg/L), No. (%)	21 (26.2)	22 (28.9)	0.72
IFX concentrations, median (IQR), µg/mL	4.4 (7.9–0)	34 (34–22.4)	<0.01
Anti-IFX antibodies, No. (%)	21 (23.3)	1 (1.1)	<0.01

Abbreviation: IBDU, inflammatory bowel disease unclassified.

respectively). A higher proportion of patients in clinical remission were identified in the HR infliximab group (>15 ug/mL) group (75% vs 38.6%, $P < 0.01$). The proportion of patients with ATI in the LR group was significantly higher than in the HR group (23.3% vs 1%, $P < 0.01$). Of the 22 patients who developed ATI, 15 had undetectable infliximab levels, 2 had measurable subtherapeutic levels (>1 ug/mL and <3 ug/mL), 4 patients had levels ranging between 5.9 and 9 µg/mL, and 1 patient had a serum infliximab concentration above the upper limit of detection of 34 µg/mL. Forty of 180 (22%) patients had infliximab concentrations above the upper limit of detection of 34 µg/mL. Undetectable (<1 ug/mL) and measurable subtherapeutic (>1 ug/mL and <3 ug/mL) infliximab concentration were observed in 20 (11.1%) patients and 5 (2.7%) patients, respectively. Details of infliximab dosing regimens in both groups are presented in Table 2.

Outcomes

Adverse effects and infections

A total of 53 AEs in 47 patients were reported in the overall cohort. In the low–serum concentration group, there were 36 AEs recorded in 30 patients, whereas in the HR group, 17 AEs were experienced by 17 patients. The proportions of patients in each group who experienced the various AEs are summarized in Table 3. The prevalence rates of infections in the low– and high–serum concentration groups were comparable (18.8% vs 12.2%, $P = 0.3$). AEs were also compared against observed IFX level quartiles using logistic regression analysis (Fig. 1). After stratifying infliximab levels by quartiles, patients in quartiles 2 (6.0–14.9), 3 (14.9–31), and 4 (>31), had a similar risk of developing an infection in comparison with patients in quartile 1 (<6.0; odds ratio [OR], 1.5; 95% confidence interval [CI], 0.53–4.69; $P = 0.42$; OR, 1.0; 95% CI, 0.31–3.18; $P = 1.0$; and OR, 0.52; 95% CI, 0.13–41.89; $P = 0.34$; respectively). An additional analysis comparing infections against 3 subgroups according to 3 ranges (<8 µg/mL, 8–20 µg/mL, and >20 µg/mL) was performed. No significant difference in the frequency of infections was observed between patients with serum infliximab levels below 8 and the 2 other subgroups (OR, 1.42; 95% CI, 0.54–3.81; $P = 0.46$; and OR, 0.56; 95% CI, 0.19–1.63; $P = 0.29$) (Fig. 2).

All together, there were 6 serious AEs, 3 in each group, all caused by infections. Infliximab was continued in all but 1 patient. Eight (4.4%) patients had to stop infliximab because of an AE, all of which were in the LR group: 3 patients for IR, 3 for drug-induced lupus reactions, and 1 for infection and 1 for loss of response (Table 4). None of the variables including sex, age, IBD subtype, smoking history, disease duration, disease activity, concomitant steroids or immunomodulators, infliximab levels, and ATI status were found to be associated with infections.

Skin Manifestations

Overall, 6.1% of the patients developed a dermatological manifestation. The frequencies of all skin manifestations and psoriatic lesions in the LR and HR groups were similar. Eight patients (4.4%) presented with new-onset psoriasis (psoriasiform reaction), all of which were categorized as mild and treated successfully with topical therapies. Three (1.6%) additional patients presented with other cutaneous lesions (2 with nonspecific skin rashes and 1 with basal cell carcinoma).

Infusion Reactions

The total number of IRs was significantly greater in the LR group (11% vs 0, $P < 0.01$, respectively). Fifty percent of IRs (5/10) were categorized as severe. Eight of the 10 patients experiencing an IR had undetectable levels with positive ATIs. The 2 other cases with an IR had a measurable therapeutic concentration (3–7 μg/mL) without the presence of ATIs. IRs were not found to be associated with duration of treatment, dosing regimen, or concomitant immunosuppression.

DISCUSSION

The correlation between infliximab levels and clinical outcomes has been confirmed in multiple studies; however, the relation between serum infliximab concentrations and the risk of AEs is still unclear. This is the first study to directly evaluate the risk of AEs and infections in patients with IBD according to infliximab trough levels. We demonstrated that the risks of infection among IBD patients receiving maintenance infliximab therapy were similar in patients with high serum concentrations as compared with lower levels. Together, these observations suggest that greater infliximab serum concentrations are not associated with a higher risk of infection and intensified dosing and, when clinically required, should not be avoided because of the concern for infection.

TABLE 2: Characteristics of Infliximab Dosing in Both Groups

	LR (n = 90)	HR (n = 90)
Dose and frequency, No. (%)	5 mg/kg, q8wk: 54 (60)	5 mg/kg, q6wk: 24 (27)
	5 mg/kg, q7wk: 21 (23)	5 mg/kg, q4wk: 20 (23)
	5 mg/kg, q6wk: 24 (26)	10 mg/kg, q6wk: 25 (28)
	5 mg/kg, q4wk: 1 (1)	10 mg/kg, q4wk: 20 (22)
Treatment duration, median (IQR), mo	24.5 (75–7.75)	25.5 (57.25–5.75)
Serum concentration, median (IQR), μg/mL	4.5 (8–0)	34 (34–22.5)

Abbreviations: LR, low-range; HR, high-range.

To achieve a more advanced therapeutic goal, such as mucosal healing, higher doses of anti-TNF therapy may be required. In a recent report, in patients with perianal disease, higher infliximab levels were associated with a higher rate of perianal fistula healing.[16] The presumably accepted concept that higher infliximab dosing would increase the infection rate has never been directly tested. In the pivotal clinical trials ACCENT 1 and ACT1/2, no difference in infection or AEs was observed across the treatment groups of 5 and 10 mg/kg.[1, 2] According to the TREAT registry, escalating the dose of infliximab from 5 to 10 mg/kg had no effect on the occurrence of serious infections.[3] In contrast, a retrospective study by Hendler et al. demonstrated that high doses of infliximab were associated with a higher rate of serious infections.[17] The higher rate of infection in the latter study was possibly confounded by the higher prevalence of severe disease in patients on high doses of infliximab. Moreover, infliximab serum levels are influenced by many factors that affect drug clearance, such as disease severity, immunogenicity, and concomitant immunosuppression. Therefore, higher doses do not necessarily correlate with higher infliximab concentrations. Thus, evaluating the association between infliximab levels and AEs is seemingly a more appropriate assessment and is one of the strengths of our study.

An agreed definition of what is considered a supra-therapeutic infliximab trough level has not been determined, although most reviews of the topic suggest that clinicians should aim for a range of 3–7 ug/mL to achieve optimal clinical outcomes. There are existing data suggesting this range to be associated with sustained clinical benefit.[8, 18] However, in patients with higher inflammatory burden such as in moderate to severe extensive ulcerative colitis or in active perianal Crohn's disease, there are existing data to suggest that a priori higher levels are needed when aiming for a more ambitious goal such as healing of the mucosa or deep remission.[16, 19] Moreover, results from various clinical trials of different biologic agents have shown that clinical outcomes can be improved through dose optimization strategies after a secondary loss of response. Despite the use of therapeutic drug monitoring, bringing infliximab to the desired level is not always an easy task. In some cases, levels cannot be optimized even with significantly higher doses. Conversely, in some cases, high levels may be reached after successful efforts to induce remission with accelerated dosing regimens. In many cases, these HR levels will raise concerns of toxicity in both clinicians and patients, prompting the decision to de-escalate the dose. In our study, we present data on very high levels that have not been presented previously in the literature, suggesting that there are no major safety concerns should levels run high. Notwithstanding this observation, there may be other considerations for de-escalation of therapy such as cost and convenience that must be individualized for each patient.

Dermatological manifestations are a common adverse event secondary to anti-TNF therapy, with psoriasiform lesions

TABLE 3: Adverse Events in Patient With Lower and Higher Levels of Infliximab

Number of Patients With Adverse Events, No. (%)	IFX < 15 ug/mL (n = 90)	IFX > 15 ug/mL (n = 90)	*P*
Adverse events, No. (%)	30 (33.3)	17 (18.8)	0.04
Serious adverse events, No. (%)	3 (3.3)	3 (3.3)	1.0
Infections, No. (%)	17 (18.8)	11 (12.2)	0.3
Serious infections, No. (%)	3 (3.3)	3 (3.3)	1.0
Opportunistic infections, No. (%)	6 (6.6)	4 (4.4)	0.74
Skin manifestations, No. (%)	5 (5.5)	6 (6.6)	1.0
Infusion reactions, No. (%)	10 (11.1)	1 (1.1)	<0.01
Other adverse events, No. (%)	4 (4.4)	0	0.12

being the most frequent presentation.[20] The pathophysiology of this phenomenon is still poorly understood. Several recent reports have failed to demonstrate an association between high infliximab levels and cutaneous adverse effects,[21, 22] suggesting that infliximab pharmacokinetics are not linked to cutaneous manifestations. Our study is consistent with previous data showing similar rates of skin AEs in patients with higher and normal levels.[23] The proportion of patients presenting with any anti-TNF-induced skin AE in our study was slightly lower in comparison with historical data. This observation may have resulted from the selected short observational period in proximity to the measured level. Despite the lower rate of cutaneous complications, our rates of psoriatic lesions correlated well with the frequencies quoted in the literature. Some studies have suggested an association between skin reactions and a lower degree of intestinal inflammation.[24] Our results were not consistent with these findings, with no apparent association between psoriasis reactions and disease activity. However, our results should probably be interpreted with caution due to the small sample size.

Infusion reactions are potentially serious adverse events related to infliximab and have been associated with high therapy withdrawal rates and reduced remission rates in the subsequent 2 years.[25] Infusion reactions have been directly correlated with the presence of ATIs in adults with CD and UC.[26]

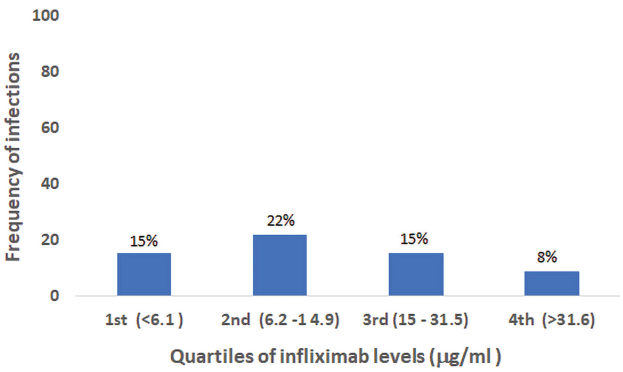

FIGURE 1. Infections by quartiles of trough levels of infliximab.

Moreover, undetectable trough infliximab concentrations were linked to a higher risk of antibody formation against infliximab.[27, 28] Both observations are confirmed in our IBD cohort. All the patients who developed an infusion reaction were from the LR group. In addition, 80% of those with infusion reactions had measurable antibodies toward infliximab. ATIs have been shown to be associated with reduced durability of therapy and worse outcomes.[26] Considerable effort is being made to determine the best strategy to prevent antibody formation. Two of these strategies were the implementation of scheduled regimens in contrast to episodic treatment and the adding of an immunomodulator. Another strategy for preventing ATI development is maintaining higher infliximab levels. The striking difference in the frequencies of IRs between the 2 groups emphasizes the probable benefit of high levels in preventing immunogenicity and therefore reducing the risk of IRs to ATIs. As antidrug antibody formation has negative clinical implications, every effort should be made to optimize the patient's drug level, which should result in improved clinical outcomes.

Both in vitro and in vivo studies have tried to identify possible mechanisms for the immune-deficient state induced by anti-TNF therapy. One of the well-known mechanisms relates to the important role of TNF-α in the formation of granulomas, which are crucial for the sequestration of mycobacteria, and in the immune response toward other granulomatous infections.[29] TNF-α can induce activation and differentiation

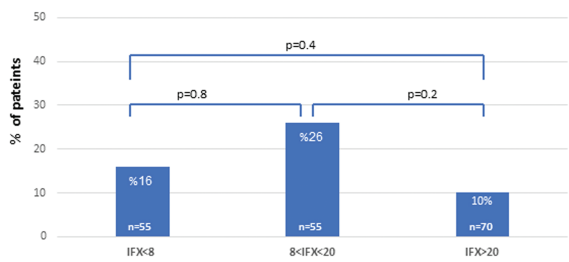

FIGURE 2. Infections among 3 groups of patients with different ranges of infliximab levels.

TABLE 4: Details of Adverse Events in Patients With Lower and Higher Infliximab Levels

	IFX < 15 ug/mL (n = 90)	IFX > 15 ug/mL (n = 90)
Infections, no.(%)	17 (18.8)	11 (11.1)
Respiratory, no.(%)	8 (8.8)	5 (5.5)
Skin infection, no.(%)	3 (3.3)	2 (2.2)
Urinary tract infection, no.(%)	0	1 (1.1)
Viral infections, no.(%)	5 (5.5)	1 (1.1)
Clostridium difficile, no.(%)	1 (1.1)	2 (2.2)
Cutaneous adverse event, no.(%)	5 (5.5)	6 (6.6)
Psoriasis, no.(%)	4 (4.4)	4 (4.4)
Nonspecific skin reaction, no.(%)	1 (1.1)	2 (2.2)
Infusion reactions, no.(%)	10 (11.1)	0
Immune reactions, no.(%)	4 (4.4)	0
Discontinuation of infliximab, no.(%)	8 (8.8)	0
Infusion reaction, no.(%)	3 (3.3)	0
Lupus-like drug reaction, no.(%)	3 (3.3)	0
Infections, no.(%)	1 (1.1)	0

of macrophages, which is critical for the clearance of intracellular pathogens (eg, Listeria, Legionella, Salmonella).[30] TNF-α is also important for immune responses against viral pathogens, and its inhibition could cause complications in patients infected with hepatitis B virus[31] or varicella zoster virus.[32] Despite these potential adverse effects on the immune response, there are no data showing any dose-dependent effect of anti-TNFs through one of these pathways. Therefore, it cannot be assumed that the risk of infection is level dependent. It is difficult to speculate on why we have not found a level-dependent association with infections, but it may be that once effective target binding has been achieved, excess circulating monoclonal antibodies do not exert a biological effect when not bound to their target.

This study must be interpreted with some caution due to its nonrandomized, retrospective design. Data collection relied on short time assessment (up to 6 months) and subjective reporting, which may have resulted in the under-reporting of relevant adverse events. We found significant differences between the 2 groups regarding age at diagnosis, age at study inclusion, and disease duration, which could have had a confounding effect on our results. Last, as the data in our study only included patients exposed to infliximab, our results may not necessarily be extrapolated as a class effect.

In conclusion, subjects with IBD and higher infliximab serum levels do not have a greater risk of infections and other anti-TNF-related AEs compared with individuals with lower serum concentrations. Higher infliximab levels are associated with a lower chance of developing ATIs and IRs. It is advisable to optimize anti-TNF therapy to target more robust endoscopic outcomes such as mucosal healing, and this may require the administration of higher doses with the possible result of higher serum concentrations of drug. Our results can be reassuring to the practicing physician that it may be more advantageous to pursue a dose optimization strategy to achieve mucosal healing rather than switching or leaving a patient undertreated due to fear of toxicity with higher doses; however, prospective trials are required to better understand how to individualize infliximab dosing and how therapeutic drug monitoring may inform this.

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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;359:1541–9.
2. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353:2462–76.
3. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol*. 2012;107:1409–22.
4. Van Assche G, Lewis JD, Lichtenstein GR, et al. The London position statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organisation: safety. *Am J Gastroenterol*. 2011;106:1594–602; quiz 1593, 1603.
5. Colombel JF, Feagan BG, Sandborn WJ, et al. Therapeutic drug monitoring of biologics for inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18:349–58.
6. Ordás I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2012;10:1079–1087; quiz e85.
7. Zittan E, Kabakchiev B, Milgrom R, et al. Higher adalimumab drug levels are associated with mucosal healing in patients with Crohn's disease. *J Crohns Colitis*. 2016;10:510–5.
8. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. *Gastroenterology*. 2014;147:1296–307.e5.
9. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology*. 2015;148:320–9.e3.
10. Colombel JF, Rutgeerts PJ, Sandborn WJ, et al. Adalimumab induces deep remission in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2014;12:414–22.e415.
11. Yarur AJ, Jain A, Hauenstein SI, et al. Higher adalimumab levels are associated with histologic and endoscopic remission in patients with Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis*. 2016;22:409–15.
12. Ungar B, Levy I, Yavne Y, et al. Optimizing anti-TNF-α therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2016;14:550–7.e2.
13. Wang SL, Ohrmund L, Hauenstein S, et al. Development and validation of a homogeneous mobility shift assay for the measurement of infliximab and antibodies-to-infliximab levels in patient serum. *J Immunol Methods*. 2012;382:177–88.
14. Hanauer SB, Wagner CL, Bala M, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol*. 2004;2:542–53.

15. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol*. 2005;19(Suppl A):5A–36A.
16. Yarur AJ, Kanagala V, Stein DJ, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2017;45:933–40.
17. Hendler SA, Cohen BL, Colombel JF, et al. High-dose infliximab therapy in Crohn's disease: clinical experience, safety, and efficacy. *J Crohns Colitis*. 2015;9:266–75.
18. Bortlik M, Duricova D, Malickova K, et al. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease. *J Crohns Colitis*. 2013;7:736–43.
19. Ungar B, Mazor Y, Weisshof R, et al. Induction infliximab levels among patients with acute severe ulcerative colitis compared with patients with moderately severe ulcerative colitis. *Aliment Pharmacol Ther*. 2016;43:1293–9.
20. Moustou AE, Matekovits A, Dessinioti C, et al. Cutaneous side effects of anti-tumor necrosis factor biologic therapy: a clinical review. *J Am Acad Dermatol*. 2009;61:486–504.
21. Coutzac C, Chapuis J, Poullenot F, et al. Association between infliximab trough levels and the occurrence of paradoxical manifestations in patients with inflammatory bowel disease: a case-control study. *J Crohns Colitis*. 2015;9:982–7.
22. Cleynen I, Van Moerkercke W, Billiet T, et al. Characteristics of skin lesions associated with anti-tumor necrosis factor therapy in patients with inflammatory bowel disease: a cohort study. *Ann Intern Med*. 2016;164:10–22.
23. Brandse JF, Vos LM, Jansen J, et al. Serum concentration of anti-TNF antibodies, adverse effects and quality of life in patients with inflammatory bowel disease in remission on maintenance treatment. *J Crohns Colitis*. 2015;9:973–81.
24. Mälkönen T, Wikström A, Heiskanen K, et al. Skin reactions during anti-tnfα therapy for pediatric inflammatory bowel disease: a 2-year prospective study. *Inflamm Bowel Dis*. 2014;20:1309–15.
25. Moss AC, Fernandez-Becker N, Jo Kim K, et al. The impact of infliximab infusion reactions on long-term outcomes in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2008;28:221–7.
26. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med*. 2003;348:601–608.
27. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. *Am J Gastroenterol*. 2013;108:962–71.
28. Baert F, Kondragunta V, Lockton S, et al. Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris Trial. *Gut*. 2016;65:1126–31.
29. Roach DR, Bean AG, Demangel C, et al. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *J Immunol*. 2002;168:4620–7.
30. Koo S, Marty FM, Baden LR. Infectious complications associated with immunomodulating biologic agents. *Infect Dis Clin North Am*. 2010;24:285–306.
31. Carroll MB, Forgione MA. Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. *Clin Rheumatol*. 2010;29:1021–9.
32. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA*. 2009;301:737–44.