Patients with Crohn's Disease with High Body Mass Index Present More Frequent and Rapid Loss of Response to Infliximab

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Background: Infliximab (IFX) is effective in inducing and maintaining remission in patients with luminal and anoperineal Crohn's disease (CD). However, treatment failure within 12 months after initiating IFX is observed in a significant proportion of patients. The aim of the present study was to determine whether the body mass index (BMI) affects response to IFX during the first year of treatment in patients with CD.

Methods: All patients with luminal CD who began IFX between January 2010 and May 2014 were prospectively included. BMI was calculated before IFX treatment was begun, and patients were divided into 3 groups: normal BMI (BMI < 25 kg/m^2), overweight patients (BMI of 25.0–30 kg/m^2), and obese patients (BMI > 30.0 kg/m^2). The primary outcome was to evaluate the rate and delay of IFX optimization during the first year of treatment among normal weight, overweight, and obese patients.

Results: One hundred forty patients were included. Demographic and clinical characteristics at IFX initiation were comparable among the 3 groups. Within 12 months after the initiation of IFX, the rate of IFX optimization was significantly higher in overweight and obese patients than in the normal BMI group: 52%, 56%, and 20%, respectively ($P = 0.0002$). The median time until optimization of IFX was significantly shorter in overweight and obese patients than in the normal BMI group: 7, 7, and 10 months, respectively ($P = 0.03$). A BMI >25 kg/m^2 was significantly associated with IFX optimization within 12 months on multivariate analysis.

Conclusion: This is the first study to show that optimization of IFX is more frequent and faster in obese and overweight patients with CD and occurs within 12 months after beginning IFX, suggesting that an induction regimen with higher doses of IFX and a tight control of IFX concentrations may be needed in these patients.

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Key words: Crohn's disease, infliximab, body mass index, therapeutic strategy

Crohn's disease (CD) is a chronic inflammatory bowel disorder with alternating periods of disease activity and clinical remission. Obtaining long-term deep remission is essential to prevent irreversible gastrointestinal damage and disability.[1,2] Several drugs are recommended to obtain long-term remission of CD, including thiopurines,[3] methotrexate,[4] and more recently, tumor necrosis factor antagonists.[5] Infliximab (IFX) is a monoclonal chimeric antibody directed against TNF-alpha that has been shown to be effective for both induction and maintenance therapy in patients with CD CD. However, 10% to 30% of the patients do not respond to initial treatment (primary nonresponse) and 20% to 45% of patients lose the response within the first 12 months after

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treatment.[6,7] Thus, treatment failure occurs in up to one-third of the patients, requiring dose escalation within the first year of treatment with IFX.

Several mechanisms can play a role in the failure of IFX treatment. The mechanism that has been the most extensively investigated is immunogenicity, which elicits antibodies that direct against the variable fragment (Fab) of the molecule. The formation of antidrug antibodies results in rapid clearance of IFX through the immune complex formation that are eliminated in the reticuloendothelial system.[6,8] IFX clearance can also be influenced by other factors such as excess weight and obesity, and several hypotheses have been suggested for this.[8] First, clearance of a drug is influenced by the volume of distribution, which is dependent on the patient's weight.[9] Second, excess adipose tissue modifies the pharmacokinetics of anti-TNF and causes endocrine and immune effects through the release of adipocytokines, which are suspected to contribute to the pathogenesis of several inflammatory conditions.[10,11] Thus, excess body weight could explain the initial failure of IFX therapy.

The aim of the present study was to evaluate whether the body mass index (BMI) affects response to IFX treatment during the first year of treatment in patients with CD.

MATERIALS AND METHODS

Study Design and Population

We performed an observational prospective study at a tertiary gastroenterology department in Lille, France. Data were prospectively collected in the inflammatory bowel disease database of the Gastroenterology Department of the University Hospital in Lille, France to identify patients with CD who had received IFX. Patients were included if they met the following criteria[1]: a diagnosis of CD based on the usual clinical, endoscopic, and histological criteria,[2] initiation of IFX treatment between January 2010 and May 2014, and[3] ≥12-month follow-up after IFX was begun.

Data Collection

The date of inclusion corresponded to the date that IFX was begun. Demographic and biological data were obtained from a prospective register managed by a resident who is a CD specialist in the gastroenterology department of the Claude Huriez Hospital, in Lille. The following data were collected at the initiation of IFX: age, gender, duration, location, and phenotype of CD according to the Montreal classification,[12] smoking status, previous intestinal resections, before exposure to CD treatment including conventional immunosuppressors (ISs) (thiopurines and methotrexate [MTX]) and anti-TNF therapies (adalimumab and certolizumab pegol), indication for the initiation of IFX (luminal or perianal CD), association with IS or corticosteroid (CT) treatments at initiation of IFX, initial Harvey–Bradshaw index (HBI) (elevated if >4), and C-reactive protein (CRP) levels (elevated if >5 mg/L). HBI and CRP were also obtained during follow-up and at 12 months. The standard regimen of IFX was an induction intravenous dose of 5 mg/kg body weight at 0, 2, and 6 weeks, followed by a maintenance regimen of 5 mg/kg IV every 8 weeks thereafter.

Definitions of BMI

BMI was calculated when IFX was begun; BMI was considered to be a continuous variable and an analysis was performed using BMI as a categorical variable, stratified according to World Health Organization (WHO) guidelines; normal weight (BMI < 25 kg/m^2), overweight (BMI of 25.0–30 kg/m^2), and obese (BMI > 30.0 kg/m^2).

Outcomes

The primary outcome was to evaluate the rate and the delay to IFX optimization during the first year of treatment in normal weight, overweight, and obese patients with CD. IFX dose optimization was defined as increasing the dosage to more than 5 mg/kg (without limit of IFX dose in patients with a weight excessed 100 kg) and/or shortening the interval between infusions to less than 8 weeks.

The secondary outcomes were to compare the following events during the first year of follow-up in the 3 groups of patients[1]: the occurrence of intestinal resections and/or perianal surgery,[2] the introduction of CT and/or IS,[3] the discontinuation of IFX therapy, and[4] the occurrence of a pejorative event defined by the occurrence of one of the previous events (IFX optimization, surgery, introduction of CT and/or IS, and/or discontinuation of IFX therapy).

Statistical Methods

A descriptive statistical analysis was performed to analyze baseline characteristics. Medians with interquartile ranges (IQR) were calculated for continuous data and percentages were computed for discrete variables. The independence of 2 variables was investigated by the Chi-square test. The Student's *t* test was performed for comparison of groups. The rates of IFX optimization were calculated for the 3 groups and compared between each group by Fisher's exact test. Univariate and multivariate logistic regression were performed to identify predictive factors of IFX optimization within 12 months, expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Variables with a *P* value below 0.20 were used for multivariate analysis. A *P* value of 0.05 was considered to be significant. Statistical analysis was performed using Stata 14 (StataCorp LP, College Station, TX).

RESULTS

Patient Characteristics

From January 2010 to May 2014, 167 active patients with CD began IFX treatment in the Gastroenterology Department of Lille University Hospital. Twenty-seven patients were excluded because of less than 12-month follow-up after the initiation of IFX. Finally, 140 patients with CD were included in the final

analysis (Fig. 1). Baseline demographic and clinical characteristics are presented in Table 1. Sixty-nine (49%) patients were men, median age at diagnosis was 25 years (IQR: 20–32), median age at the initiation of IFX was 32 years (IQR: 25–42), and median time from the diagnosis of CD to inclusion was 53 months (IQR: 9–157). The median BMI at baseline was 22 kg/m^2 (IQR: 20–27). BMI distribution among the patients was the following: 96 (69%) in the BMI group <25 kg/m^2, 21 (15%) in the overweight group, and 23 (16%) in the obese group (Fig. 2). The indication for the initiation of IFX was luminal CD in 108 patients (77%), and perineal disease in 32 (23%). When IFX was initiated, the median HBI, obtained in all patients, was 6 (IQR: 4–8); and the median CRP, obtained in 135 (96%) patients, was 10 mg/L (IQR: 4–25) including 89 (66%) patients with a CRP > 5 mg/L. The disease characteristics at the initiation of IFX were comparable in the 3 groups for smoking status, phenotype, and location at diagnosis according to the Montreal classification, clinical disease activity assessed by HBI, CRP, the use of IS treatment, and previous intestinal resections. However, overweight and obese patients were statistically older than patients with normal BMI at diagnosis and when IFX was initiated (28, 32, and 23 yr; respectively: $P <$ 0.05 and 35, 43, and 29 yr, respectively: $P < 0.05$), with no difference between overweight and obese patients ($P = 0.19$).

Rate and Delay to IFX Optimization

IFX optimization was necessary in 43/140 patients (31%) within 12 months after the initiation of IFX. The median time to optimization was 8 months (IQR: 5–10). The main regimens of optimization were an increase in the dose of IFX of 10 mg·kg^{-1}·8 wk^{-1} in 14 patients (33%), 5 mg·kg^{-1}·4 wk^{-1} in 14 patients (33%), 5 mg·kg^{-1}·6 wk^{-1} in 10 patients (23%), and 5 mg·kg^{-1}·7 wk^{-1} in 5 patients (12%). The reasons for optimization were a primary inefficiency in 15 (35%) patients and loss of response in 27 (63%), defined by a significant deterioration of clinical and biological parameters of CD. One (2%) patient was optimized for extradigestive symptoms. There was no significant difference among the 3 groups for the reasons for optimization. The reasons and regimens of optimization are shown in Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B544. Thirty (70%) patients had a CRP > 5 mg/L at optimization, with a median CRP of 11 (IQR: 5–19) mg/L (10, 12, and 9 mg/L for BMI< 25 kg/m^2, in overweight, and obese patients, respectively), with no statistical difference between the 3 groups ($P = 0.5$).

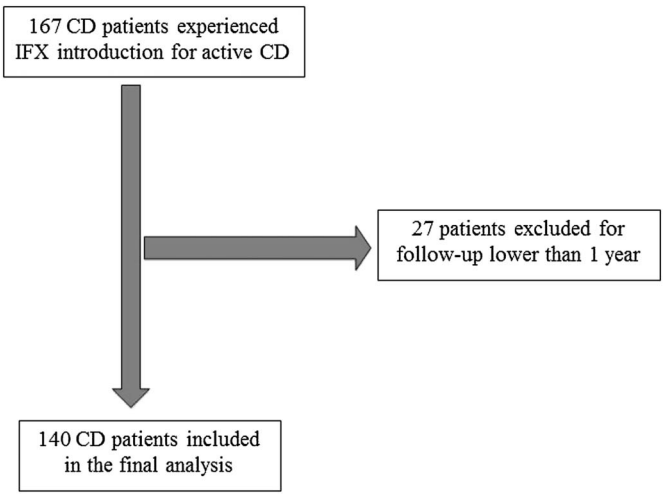

FIGURE 1. Flowchart of patients' inclusion.

Within 12 months after the initiation of IFX, the optimization rate was significantly higher in overweight and obese patients than in the normal BMI group: 11/21 (52%), 13/23 (56%), and 19/96 (20%) patients, respectively ($P = 0.0044$ and $P = 0.0011$, respectively) (Fig. 3). The median delay to IFX optimization was significantly shorter in overweight and obese patients than in the normal BMI group: 7 (IQR: 5–9), 7 (IQR: 5–10), and 10 (IQR: 6–11) months, respectively ($P = 0.01$ and $P = 0.03$, respectively) (Fig. 4). There was no significant difference between overweight and obese patients for the rate and time to IFX optimization ($P = 1.00$ and $P = 0.93$, respectively).

The independent predictive factors of IFX optimization within 12 months on univariate and multivariate analyses are shown in Table 2. On multivariate analysis, a BMI >25 kg/m^2 (OR: 3.38, 95% CI [1.56–7.35]; $P = 0.002$), a HBI > 5 at the initiation of IFX (OR: 2.49, 95% CI [1.17–5.29]; $P = 0.02$), and age at the initiation of IFX >32 years (OR: 2.22, 95% CI [1.04–4.77]; $P = 0.04$) were significantly associated with optimization within 12 months.

Occurrence of a Pejorative Event Within 12 Months After IFX Initiation

Within 12 months after IFX was begun, 13/140 (9%) patients required an intestinal resection including 4/140 (3%) who required perianal surgery. The introduction of CT and/or IS treatment was observed in 21/140 (15%) patients. IFX was withdrawn in 10/140 (7%) patients. At the end, the occurrence of a pejorative event was observed in 78/140 (56%) patients.

There was no significant difference between normal, overweight, and obese patients for the rate of bowel resection and/or perianal surgery: 9/96 (9%), 1/21 (5%), and 3/23 (13%), respectively ($P = 0.64$); the rate of IFX withdrawal: 4/96 (4%), 3/21(14%), and 3/23 (13%) ,respectively ($P = 0.13$); the rate of introduction of CT and/or IS: 13/96 (14%), 5/21 (24%), and 3/23 (13%), respectively ($P = 0.47$). The occurrence of a pejorative event indicated because of the occurrence of one of the previous events (IFX optimization, surgery, introduction of CT and/or IS, or withdrawal of IFX) was significantly higher in overweight patients (18/21 [86%]) and in obese patients (19/23 [83%]) than in the normal BMI group (41/96 [43%]), (respectively, P 0.0005 and $P = 0.0009$). There was no significant difference between overweight and obese patients for the occurrence of a pejorative event ($P = 1$) (see Supplemental Figure 1, Supplemental Digital Content 2, http://links.lww.com/IBD/B545).

TABLE 1. Demographic and Clinical Characteristics at IFX Start (n = 140)

	Whole Population	BMI < 25	25 < BMI < 30	BMI > 30	*P*
Male sex, n (%)	69 (49)	49 (51)	9 (43)	11 (48)	
HBI at IFX initiation (IQR)	6 (4–8)	6 (4–7)	6 (4–8)	6 (3–8)	0.98
Median age at diagnosis (IQR), yr	25 (20–32)	23 (20–29)	28 (22–36)	32 (26–40)	**0.0003**
Median age at introduction IFX (IQR), yr	32 (25–42)	29 (23–38)	35 (28–44)	43 (36–48)	**0.0011**
Current smoking, n (%)	45 (32)	31 (33)	6 (29)	8 (35)	0.9
Median disease duration (IQR), yr	53 (9–157)	54 (8–150)	50 (19–166)	54 (11–170)	0.8
CD location (Montreal classification), n (%)					0.67
L1 (isolated ileal disease)	47 (34)	34 (35)	6 (28)	7 (30)	
L2 (isolated colonic disease)	27 (19)	18 (19)	2 (10)	7 (31)	
L3 (ileocolonic disease)	66 (47)	44 (46)	13 (62)	9 (39)	
CD behavior (Montreal classification), n (%)					0.95
B1 (non B2–non B3)	83 (60)	56 (59)	13 (61)	14 (61)	
B2 (stricturing)	35 (25)	24 (25)	5 (25)	6 (26)	
B3 (penetrating)	13 (9)	9 (10)	3 (14)	1 (4)	
Penetrating and stricturing	8 (6)	6 (6)	0 (0)	2 (9)	
P (perianal disease), n (%)	46 (33)	32 (33)	7 (33)	7 (33)	0.49
Previous anti-TNF treatment, n (%)	31 (22)	24 (25)	4 (19)	3 (13)	0.43
Previous immunosuppressant, n (%)	81 (57)	53 (51)	16 (76)	12 (52)	0.17
Previous intestinal resection, n (%)	56 (40)	40 (41)	7 (33)	9 (39)	0.77
Concomitant immunosuppressant, n (%)	69 (49)	48 (50)	11 (52)	10 (43)	0.78
Reason for IFX introduction, n (%)					0.85
Luminal disease	108 (77)	74 (77)	17 (81)	17 (74)	
Anal disease	32 (23)	22 (23)	4 (19)	6 (26)	
Median BMI (IQR), kg/m^2	22 (20–27)	20 (19–22)	27 (26–28)	31 (31–35)	
CRP > 5 mg/L at IFX initiation, n (%)	89 (66)	62 (68)	15 (71)	12 (52)	0.34
Median CRP level at IFX initiation (IQR), mg/L	10 (4–25)	10 (5–31)	7 (5–11)	9 (2–22)	0.30

HBI, Harvey–Bradshaw index; TNF, tumor necrosis factor.
Bold indicates statistically significant differences between the 3 groups.

DISCUSSION

Several recent studies have reported a significant rate of IFX optimization with a primary nonresponse and an early secondary loss of response in more than one-third of patients during the first year after the initiation of IFX.[6,7,13] This study confirms these results, with 31% of patients with CD treated with IFX who required dose optimization within the first year of

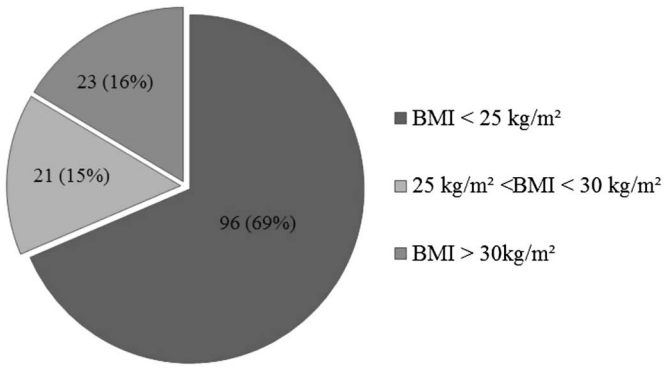

FIGURE 2. Distribution of patients according to BMI (N = 140).

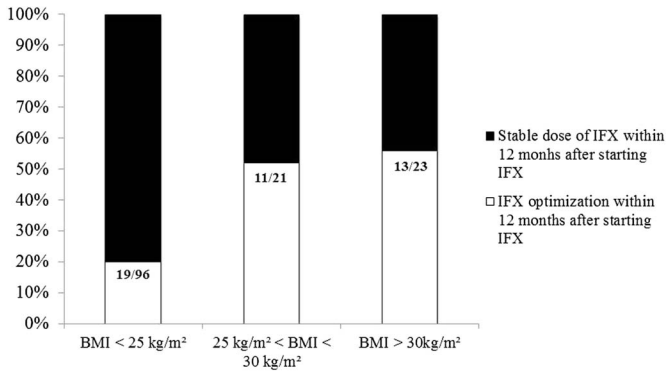

FIGURE 3. IFX optimization rates within 12 months after IFX introduction among normal weight, overweight and obese patients.

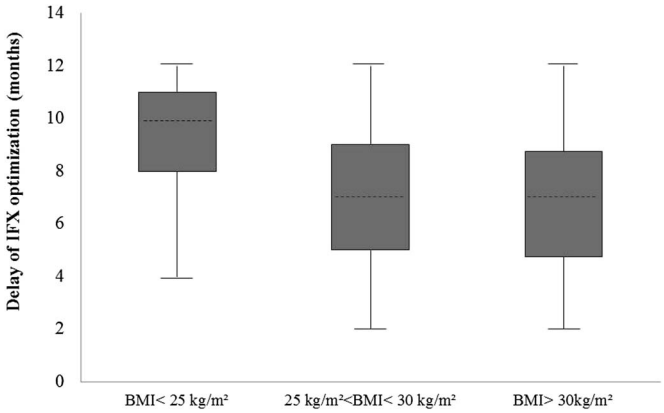

FIGURE 4. Box plots of median delay of IFX optimization after IFX introduction among normal weight, overweight, and obese patients. The box represents the 25th to 75th percentiles, the whiskers correspond to the 5th to 95th percentiles, and the dotted lines within boxes are median values.

treatment, a median of 8 months after the initiation of IFX. It is interesting to note that an attenuated response to IFX in CD was found in overweight and obese patients, with faster and more frequent optimization of IFX in these groups. Our results suggest that overweight and obese patients with CD with more adipose tissue could have a more severe inflammatory course to their disease and require a more aggressive therapeutic strategy to avoid a primary nonresponse or an earlier secondary loss of response. These results are important because of the increasing prevalence of obesity worldwide especially in the Western Countries; in France, 32% of adults are categorized as overweight and 15% as obese.[14] In CD, the prevalence of overweight patient is even higher with 32% to 52% of patients with CD considered to be overweight or obese.[15,16] We also showed that age at the initiation of IFX >32 years was significantly associated with a need of IFX optimization within 12 months. This is consistent with the results of the study performed by Juillerat et al,[17] reporting that an age ≤33 years at start of IFX was associated with a beneficial long-term use of IFX in CD.

Previous studies have shown that obese patients with CD more frequently have active disease, require hospitalization, and have anoperineal disease than their normal-weight peers.[18] The time to first CD-related surgery is also reduced in overweight and obese patients with CD than in patients with a BMI <18.5 kg/m^2 (252 mo versus 24, respectively, $P = 0.043$).[19] It has been reported that fat mass may also affect the response to IFX therapy in other immune-mediated inflammatory diseases.[20] In rheumatoid arthritis, Klassen et al[21] have shown a negative correlation between BMI and clinical response to IFX. The results in another study in patients with ankylosing spondylitis treated by IFX were similar to a negative influence of BMI >25 kg/m^2 on clinical and biological response at 6 months. BMI was identified as an independent risk factor for a poor response at M6 on multivariate analysis, whatever the response criteria (Bath Ankylosing Spondylitis Disease Activity Index, CRP).[22] Similarly, in psoriasis, obesity was considered as the clinical predictor of nonresponse to IFX therapy.[23] Moreover, obesity was associated with an increased probability of biological treatment withdrawal.[24]

Only few studies have focused on the response of anti–TNF-α in overweight or obese patients with CD in inflammatory bowel disease. A North American study on IFX including 124

TABLE 2. Univariate and Multivariate Logistic Regression Analyses of Predictors of IFX Optimization Within 12 Months After Starting IFX (n = 140)

Factors Predicting IFX Optimization Within 12 mo After Starting IFX	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
Female sex	1.56 (0.56–4.32)	0.38		
Age at IFX introduction > 32 yr (median)	2.22 (1.02–4.84)	0.04	**2.22 (1.04–4.77)**	**0.04**
Disease duration > 53 mo (median)	1.91 (0.89–4.11)	0.09	1.91 (0.90–4.06)	0.09
Smoking status at IFX introduction	1.08 (0.49–2.37)	0.86		
Perianal disease	1.41 (0.65–3.07)	0.38		
Previous surgery resection	0.58 (0.26–1.27)	0.17	0.58 (0.26–1.26)	0.17
Previous anti-TNF treatment	1.90 (0.80–4.50)	0.13	1.92 (0.83–4.46)	0.13
Previous immunosuppressant	1.60 (0.74–3.50)	0.23		
HBI > 5 at IFX initiation	2.49 (1.15–5.39)	0.02	**2.49 (1.17–5.29)**	**0.02**
CRP > 5 at IFX initiation	1.60 (0.76–3.40)	0.21		
Concomitant immunosuppressant	0.50 (0.23–1.08)	0.07	0.50 (0.24–1.07)	0.07
BMI > 25 kg/m^2	3.38 (1.50–7.59)	0.002	**3.38 (1.56–7.35)**	**0.002**
CT at IFX initiation	1.90 (0.86–4.30)	0.11	1.90 (0.86–4.18)	0.86

Bold value indicates statistically significant odds ratios in the multivariate analysis.
HBI, Harvey–Bradshaw index.

patients (CD and ulcerative colitis) found that a higher BMI was associated with an increased risk of a CD flare defined as IFX dose escalation, CT use, discontinuation of IFX, and/or hospitalization or surgery.[13] That study was limited by the heterogeneous population (including patients with CD and ulcerative colitis) and the long duration of follow-up (3 yr), leading to a risk of a change in the BMI because IFX treatment can cause weight gain[25,26] and increases visceral fat deposition.[27] On the contrary, a recent study by Brown et al[28] assessed the response to IFX in 388 patients with CD and reported that an increase in BMI was associated with a reduced risk of loss of response and CD-related surgery within 12 months after the initiation of IFX. However, this study had several limitations. In particular, obese patients were excluded from the analysis, all patients from 1999 to 2012 treated with different regimens of IFX administration (intermittent and continuous) that do not reflect current use, were included, and smoking status, an important factor in maintaining remission,[29,30] was not determined. One of the strengths of our study is the follow-up 12 months after the initiation of IFX which reduces the potential risk of bias from changes in BMI status over time. Furthermore, the population only included patients with CD, with a large group of patients included for a limited 4-year period (2010–2014). Finally, this was the first study to report that BMI >25 kg/m^2 is a predictive factor of IFX optimization within 12 months after starting treatment in patients with CD on multivariate analysis. It has recently been shown that the optimization of IFX in patients with CD within the first year after starting treatment is an independent predictor of IFX failure-free survival over time.[31] These results strongly suggest that overweight and obese patients with CD may require close monitoring of response and remission after the initiation of IFX. Moreover, weight gain is frequent on IFX in patients with psoriasis, even in patients with BMI <25 kg/m^2. Although there are no available data in CD, weight gain should be monitored in IFX-treated patients because it may lead to a secondary loss of response.[32]

Further findings could explain the negative influence of a high BMI on IFX response. Obesity is a pro-inflammatory condition that contributes to increase circulating levels of pro-inflammatory cytokines. In ex vivo studies, adipocytes from obese humans and animals have been shown to express higher amounts of TNFα than nonobese controls.[33] As elevated circulating levels of TNFα have been shown to lead to a diminished responsiveness to IFX[34] with low IFX trough concentrations and high rates of antibodies formation,[35,36] we can speculate that pro-inflammatory state related to increased adiposity could partially explain the attenuated response to anti-TNF agents in heavier individuals. In a recent study, it has been reported that obese individuals had lower 6-thioguanine (6-TGN) levels than their nonobese counterparts when adjusted for the total received dose of azathioprine or mercaptopurine relative to total body weight. The rate of subtherapeutic 6-TGN levels in individuals with BMI >25 kg/m^2 was nearly 2-fold higher than normal BMI individuals.[37] These results underline that drug metabolism is probably influenced by patient's weight and could explain the diminished efficacy of IFX treatment in obese and overweight patients with CD.

The major limitation of our study is the retrospective analysis of the data. However, the data were obtained from a prospective registry managed by the resident who is a CD specialist in the Gastroenterology Department of the Lille University Hospital and collected during the patient assessment and IFX administration. Moreover the primary outcome, rate, and delay of IFX optimization are objective and less prone to bias. Even though concomitant immunosuppressive therapy improves IFX response in patients with CD, only 50% of the patients with CD in our study received concomitant immunosuppressive therapy. This is explained by the fact that in the early inclusion period (2010), combination therapy was not common as data from the SONIC study had just become available.[38] Nevertheless, it is important to note that no significant difference was observed among the 3 groups concerning concomitant use of IS treatment. Finally, IFX trough serum concentrations and antibodies against IFX rates were not available. Some studies have suggested that low IFX serum concentrations and high anti-IFX antibody levels are associated with a more frequent loss of response in patients with CD.[39] It would have been interesting to compare IFX trough levels in relation to the BMI among the 3 groups which could modify the distribution volume and pharmacokinetics of anti–TNF-alpha through release of adipocytokines.

In conclusion, overweight and obese patients with CD present more frequent and faster IFX optimization, suggesting that an induction regimen with higher doses of IFX may be required in these patients and that close monitoring of residual IFX concentrations should be performed. Further investigations, including prospective trials with monitoring of IFX trough level and IFX antibodies are needed to assess the best therapeutic management in overweight and obese patients with CD.

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