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Running Title: Infliximab exposure and infection

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Word count (excluding title page, abstract, references, figures and tables) : 3448

Conflicts of Interest: GB received lecture fees from Abbvie, Ferring, MSD, Takeda and Pfizer and consultant fees from Takeda, Janssen. **LS** received lecture fees from Abbvie, Ferring and MSD. LS received consultant fees from Takeda and Ferring. **CB** received lecture fees from Ipsen. **AP** received lecture fees from Hospira. **AL, CM, MD** and **EB** declare no conflict of interest.

Authors' contributions: conception and design of the study: AL, GB ; acquisition of data: AL, CM, LS, CB, MD, EB, AP, GB ; analysis and interpretation of data AL, GB, AP ; drafting the article: AL GB ; and revising it critically for important intellectual content: all authors. The manuscript was approved by all authors.

Acknowledgment : none

Guarantor of the article: Guillaume BOUGUEN

Source of Funding: None

ABSTRACT

Background & Aims: Infliximab increases the risk of infection in patients with inflammatory bowel diseases (IBD), but there is controversy over the relationship between drug concentration and infections. We aimed to assess factors associated with infection in infliximab-treated patients, including pharmacokinetic features.

Methods: We collected data from 209 patients with IBD (102 men; mean age, 39 y; 159 with Crohn's disease; 54 received combination therapy) who received a infliximab maintenance regimen from November 2016 through April 2017 in France. Data were collected from each infusion visit (total of 640 infusions). Infliximab exposure was estimated based on the area under the curve (AUC) of drug concentration in pharmacokinetic models; individual exposures over the 6-month period were estimated based on the sum of the AUC (ΣAUC).

Results: The mean infliximab trough level was 5.46 mg/L, and the mean ΣAUC was 3938±1427 mg d/L. A total of 215 infections were collected from the 640 infusion visits; 123 patients (59%) had at least 1 infection. Factors independently associated with infection after multivariate analysis were smoking (odds ratio [OR], 2.05; *P*=.046), IBD flare (OR, 2.71; *P*=.006), and a high ΣAUC of infliximab (above 3234 mg x d/L) (OR, 2.02; *P*=.02). The ΣAUC was higher in patients with an occurrence of infection (*P*=.04) and correlated with the number of infections (*P*=.04). Trough concentration of infliximab alone was not associated with infection.

Conclusions: Almost two-thirds of patients treated with infliximab developed an infection; risk was individually correlated with cumulative increase in drug exposure, but not infliximab trough level.

KEY WORDS: tumor necrosis factor, anti-TNF, treatment, CD

INTRODUCTION

Although the efficacy of TNF antagonists for the treatment of inflammatory bowel disease (IBD) is widely observed,(1,2) a number of concerns remain regarding potential serious adverse events, especially infections and malignancies.(3) Recently, data from the TREAT registry (The Crohn's Therapy, Resource, Evaluation, and Assessment Tool), a large US-based prospective registry of patients with Crohn's disease (CD), indicated an increased risk of serious infection with infliximab, but not with immunomodulators.(5) In a nationwide population-based study involving French IBD patients,(6) anti-TNF monotherapy was associated with a higher risk of serious, bacterial and mycobacterial infections compared to that in patients unexposed to immunosuppressant as well as patients treated with thiopurine monotherapy. The combination therapy was associated with an even higher risk of serious and opportunistic infection compared to monotherapy with either anti-TNF or thiopurine. This may be explained by the own effect of each immunosuppressant but also by the increase of infliximab exposure related to a lower clearance when added to an immunosuppressant.(7)

Regarding this increased risk of infection with anti-TNF treatment, no clear relationship between the degree of drug exposure and this risk was observed. Therapeutic drug monitoring (TDM) with trough levels of infliximab (TLI) is considered a promising tool to guide dose adjustments of anti-TNF treatment because of a strong association between TLI and treatment efficacy.(8-10) A TLI above 5 µg/mL during maintenance therapy is consensually admitted to be associated with clinical remission with a possible concentration-response effect according to the outcome measure, regardless of the occurrence of side effects.(11–13) A first report in spondyloarthritis observed an increased risk of a first infectious event for patients treated with infliximab with recurrent high TLI (mean of the last 3 trough >11.3 µg/mL).(14) However, that result was not reproduced in a recent cohort study of IBD patients, which observed similar rates of infectious events between patients with TLI above or below 7 µg/mL.(15-16) The latter studies were unfortunately retrospective, with a large amount of lacking data and irregular follow-up that precluded an assessment of the true exposure to the drug. In these studies, the exposure to infliximab was approximated by the TLI. However, the same value of TLI may reflect different exposures to the drug, depending on the treatment modalities (dose and infusion interval). The actual exposure over a treatment period can be estimated by the cumulated area under the concentration curve. To date, the relationship between exposure and the occurrence of infection has never been explored.

Thus, the present study aimed to assess the relationship between exposure to infliximab and the risk of infection in IBD patients under a maintenance regimen as well as predictors of infectious events.

MATERIAL AND METHODS

STUDY POPULATION

From the 1st November 2016 to the 30th April 2017, data from all adult patients with an established diagnosis of CD or ulcerative colitis (UC) and treated with infliximab in a single centre were prospectively recorded over this six-month period.(supplementary Method) For the current study, all patients receiving infliximab therapy for at least four months (maintenance regimen) and without infliximab discontinuation during the study period were included.

The disease activity was assessed using the Harvey-Bradshaw Index (HBI) (18) for CD and the Partial Mayo score (PMS) (19) for UC. The clinical remission was defined by an HBI < 4 for CD or a PMS < 2 for UC. Active disease for a patient was defined as at least one clinical relapse during the study period, corresponding to at least one recorded HBI ≥ 4 or PMS ≥2.

Infectious events were reported by the patients at each infliximab infusion and were categorized by localization and type of pathogenic organisms according to a systematic questionnaire; rhinolaryngological infections were considered bacterial when an antibiotic treatment was used. Infections related to CD, such as (perianal) abscesses were not considered. All infectious events were reviewed by two investigators (AL, GB).

The TLI was measured with an in-house enzyme-linked immunosorbent assay (ELISA) fully validated following the FDA guidelines for bioanalytical analysis,(20) just before infliximab administration. The intra-day and inter-day bias (relative error) and precision (coefficient of variation) of the method were below 20%.

Patients were willing to be registered in a prospective database for research use, and the study was approved by the “Commission Nationale Informatique et Liberté” (CNIL No1412467). all authors had access to the study data and reviewed and approved the final manuscript.

EXPOSURE DETERMINATION

Because of the multiple infliximab infusion modalities that exist in a real-world cohort of IBD patients, the same value of TLI can be found in patients with different exposures as assessed by the area under the concentration-time curve (AUC), as illustrated in Figure 1. Therefore, we estimated the actual exposure to infliximab over the study period by calculating the cumulated AUC (ΣAUC) (21) (supplementary material). The ΣAUC over the observation period was obtained by summing the AUCs of all the infusions of the study period in a given individual. AUCs were derived from the individual clearances that can be accurately estimated from the trough concentrations by pharmacokinetic modelling. Therefore, no other concentration measurement was required for AUC estimation. Pharmacokinetic modelling was conducted with Monolix 4.3.3. (Lixoft, France).

END POINTS

The primary end point was factors associated with the occurrence of at least one infection over the study period. Secondary end points were factors associated with infectious events between infusions and factors associated with higher ΣAUC of infliximab.

STATISTICS

Quantitative variables were described as the mean ± standard deviation (S.D.). Categorical variables were presented as counts and percent of the cohort. For group comparisons, univariate analysis was performed using the Wilcoxon test for quantitative variables, and a chi-square test (or Fischer test as appropriate) was used for qualitative variables. All significant variables with a p-value <0.2 at the univariate step were integrated into a binary logistic regression model for multivariate analysis. When considering the continuous variables for multivariate analysis, cutoff values were determined by using receiver operating characteristic (ROC) analysis to reduce the risk of bias related to arbitrarily defined cutoffs and to identify the optimal cutoff by using each outcome as a classification variable. A p-value <0.05 was considered significant. Statistical analyses were performed using JMP Pro 13.2 software (SAS Institute Inc., Cary, NC).

RESULTS

STUDY POPULATION

A total of 288 adult IBD patients were treated with infliximab during the study period. Among them, 245 patients were treated for at least 4 months at baseline and were under a maintenance regimen. During the 6-month follow-up, 36 patients discontinued infliximab infusions for various reasons and were excluded. None of the 36 patients excluded from this analysis discontinued infliximab for infectious reason. Finally, 209 patients were included in the current study (Figure 2). The baseline characteristics of the patients are depicted in Table 1.

INFLIXIMAB INFUSIONS AND DISEASE OUTCOME DURING THE STUDY PERIOD

A total of 640 infusions were administered to the 209 patients. Each patient had a mean of 3.1 (±0.7) infusion visits during a mean follow-up of 24.7 (±3.5) weeks.

Regarding the scheme of infliximab infusions (Supplementary Table 1), 100 (48%) patients at baseline were treated with the classical maintenance regimen of 5 mg/kg every 8 weeks. The treatment regimen was optimized in dose and/or frequency for 64 (31%) patients. A longer dosing interval was ongoing for 42 (20%) patients, and 3 (1.4%) patients had an alternative treatment scheme with a longer interval but a higher dose of infliximab. Among the study population, 176 (84%) patients maintained the same treatment regimen over the study period. Optimization or de-escalation of the infliximab regimen was performed in 17 (8.2%) and 16 (7.7%) patients, respectively.

A sustained clinical remission of IBD was observed in 152 (73%) patients. Among the 57 (27%) patients who had at least one period of active IBD (HBI ≥4 or PMS ≥3), 9 (16%) had chronic active disease, whereas 48 (84%) experienced one or more clinical relapses. Clinical disease activity was reported in 83 infusion visits (13% of 640), corresponding to mild disease (4≤ HBI <9 or 2≤ PMS <5), moderate disease (9≤ HBI ≤12 or 5≤ PMS ≤7) or severe active disease (HBI >12 or PMS >7) in 82% (68/83), 14% (12/83) and 3.6% (3/83), respectively. Only five patients received glucocorticoids during the study period. (Supplementary Table 1)

Biological data indicated a mean TLI of 5.5 (±4.3) µg/mL and a mean albumin concentration of 43.6 (±2.8) g/L. The mean ΣAUC of infliximab per patient was calculated at 3938 (±1427) mg/dL.(Supplementary Table 2) A higher ΣAUC of infliximab (>3234 mg.d/L) was more frequently observed in recently treated patients (p=0.03) and in patients receiving combination therapy (p=0.02). It was also linked to a higher dose of infused infliximab (p<0.0001), a shorter interval between infusions (p=0.0003) and a higher TLI over the observation period (p<0.0001). (Supplementary Table 3)

INFECTIOUS EVENTS

A total of 222 infections were reported among the 640 infusion visits and 215 infections were retained, corresponding to 205.7 infections per 100 patient-years. No serious infection was observed. At least one infectious event was documented in 59% of patients (123/209). Broadly two-thirds of infections were viral (67%), 29% were bacterial and 9% were fungal. The main sites of infection were the ear, nose and throat (ENT - 122 infections [52%]). Most bacterial infections were related to the ENT for 43% (27/63) of reported infections, and 33% (21/63) were mucocutaneous. Among the 143 viral infections, two-thirds were related to the ENT (93 [65%]), 17% (25) were gastroenteritis and 13% (18) were influenza or influenza-like illnesses. Fungal infections were urogenital in 75% (6/8). The characteristics of infections are presented in Table 2.

FACTORS ASSOCIATED WITH INFECTION

The risk of infection was studied for each patient over the 6-month period (Table 3). The use of systemic corticosteroids was not considered for statistical purposes (only 5 cases). No difference in the rate of infections was observed according to the type of IBD (58% of patients with CD [92/159] and 62% of patients with UC [31/50]). After multivariate analysis using dichotomized variables, ongoing smoking (OR=2.05; CI95[1.01-4.16]; p=0.046), active disease (OR=2.71; CI95[1.32-5.54]; p=0.0060) and a high ΣAUC (>3234 mg.d/L) (OR=2.02; CI95[1.11-3.65], p=0.020) were significantly associated with an increased risk of infection.

Regarding the disease activity, patients with active disease were more likely than patient in clinical remission to have a high ΣAUC >3234 mg.d/L (43 *versus* 13 patients, p=0.005). They were also more likely to have an optimized infliximab treatment by either increasing the infused dose or decreasing the interval between two injections (p=0.01). When stratifying patients based on disease activity, the risk of infection remained significantly associated with a high ΣAUC among patients in sustained clinical remission over the study period (61% of patients with ΣAUC >3234 mg.d/L experienced any infection *vs* 41%, p=0.01), whereas no significant association between the risk of infection and ΣAUC was found in flaring up patients (p=0.64). There was a strong correlation between the number of infections over the study period and the decile of cAUC (supplementary Figure 3)

Further analysis of the association between ΣAUC of infliximab and the different components of infection were performed. The mean ΣAUC of infliximab was significantly higher among the group of patients with infections (4105.5 [±1476.6] *versus* 3697.9 [± 1324.9] mg.d/L, p=0.04) (Figure 3). Moreover, the ΣAUC was significantly and positively correlated with the number of infections (p=0.04) (Figure 3), the number of viral infections (p=0.04) and was also linked to the occurrence of any viral infections (p=0.01). The ΣAUC was not associated with a higher risk of bacterial infections (p=0.26), the need for antibiotics (p=0.05) nor with fungal infections (p=0.08).

When considering the link between TLI and the occurrence of at least one infection between two infusion visits (Supplementary Figure 2), no association was observed across the 640 infusion visits

during the study period: mean TLI of 5.46 (±4.28) mg/L among the 435 infusion visits without infectious events and 5.48 (±4.30) mg/L for the 135 infusion visits with the report of an infectious event since the last infusion (p=0.83).

DISCUSSION

In the present study, a higher cumulative exposure to infliximab was significantly associated with a two-fold increase in the risk of infection in IBD patients. Our data are in line with the retrospective report by Bejan-Angoulvant et al.(14) involving 201 infliximab -treated patients with spondyloarthritis. Although they did not assess the ΣAUC, authors took into account the mean of the last 3 consecutive TLIs greater than the median (>11.3 µg/mL) that somewhat reflected high exposure to infliximab. In our cohort of 209 IBD patients treated with an infliximab maintenance regimen and followed for a predefined period of time, almost two-thirds of patients (123 [59%]) experienced at least one infectious event, and 215 infections were reported among the 640 infusion visits. This is in line with the prevalence of infection observed in randomized controlled trials: in the SONIC trial,(22) infections of any type occurred in 46.0% of infliximab -treated patients.

The first data about infections in IBD patients treated with infliximab from the phase 3 trials suggested there was no increase in infections compared to placebo.(4) Of note, these trials are powered to assess the efficacy but not the safety of the treatment. More recent studies detected an increased risk of serious and opportunistic infections with infliximab treatment compared to treatment with other non-biological medications in CD, with an even higher risk associated with combination therapy. (5,6) Most available data on infections with infliximab in IBD patients compared infliximab to placebo(4) or to another conventional non-biological medication,(5,6) while the relationship between the risk of infection and the serum infliximab concentrations remains unclear. Contrary to Bejan-Angoulvant et al.,(14) two studies of the safety of infliximab in IBD patients found no increased occurrence of infection with high TLI (> 7 or 8 µg/mL).(15,23) However, the study design of both studies was not adapted to assess this relationship, and only one value of TLI was used to assess the risk of infection over a four- or six-month period. Interestingly, we found no association between TLI and the occurrence of infections between the two infusions. This suggests that the TLI remains insufficient to assess the long-term drug exposure required to find an association.

Knowing that highly exposed patients have a greater risk of infection suggests de-escalating infliximab dosage (by decreasing the dose or increasing the infusion interval) according to disease activity. A recent retrospective study of IBD patients observed a cumulative rate of relapse of 16% at one year after infliximab de-escalation,(24,25) which is three times less than after infliximab discontinuation. Furthermore, the authors suggest that a TLI-based strategy for de-escalation among selected patients in deep remission may reduce the risk of low infliximab exposure and relapse. Moreover, the present pharmacokinetic approach suggests some way to adapt infliximab treatment: for a similar TLI, adjustment of the interval rather than the dose infused would result in lower ΣAUC.

The main strength of this work was to use the ΣAUC to assess infliximab exposure. This is the first study dedicated to investigating the risk of infection with infliximab therapy that used the cumulated

AUC over a predefined period of time rather than punctual TLI.(14,15) A pharmacokinetic modelling was performed for computation of the ΣAUC of infliximab for each patient. Due to the different infliximab treatment modalities, in terms of dose and dosing interval, two patients can have the same TLIs but different levels of drug exposure, corresponding to different values of AUC. Additionally, the AUC improves the assessment of the individual exposure to a drug compared to the trough concentration. Moreover, the ΣAUC was currently taken into account to encompass the 6-month period of exposure to the drug, while the TLI only partially reflects the exposure from the last infusion.

Some limitations need to be taken into account. Monoclonal antibodies pharmacokinetics is known to follow a 2-compartment model. However, because our data were constituted only from TLI, the estimation of the distribution phase was not possible. Therefore, we chose to keep a 1-compartment model for the estimation of the AUC, which may lead to overestimate actual drug exposure. However, the objective of this work was to explore whether the exposure could be linked to the risk of infection. In this regard, as long as the method used for the estimation of the AUC is the same in all the patients of the study, the systematic over-estimation bias does not impact the main result, that is a higher cumulated exposure over a period is associated with a higher rate of infection. In addition, the results were similar using other pharmacokinetic models. Contrary to Bejan-Angoulvant and colleagues, the infliximab exposure (AUC) during a period of time was taken into account rather than the first infection following infliximab treatment that may question the causality. Of note, not only the occurrence of an infection but also the number of infections was increased in the present study. The ΣAUC has to precede the infection for being the cause of the infection. In this prospective work, infectious events were self-reported, introducing a risk of memory bias. However, in a pooled analysis across the five pivotal phase 3 IBD trials,(4) the infection rate was estimated at 49.8% in all infliximab -treated IBD patients, which is slightly less than the incidence of 59% in the current study and underlines the exhaustive declaration of infections. Furthermore, we prospectively collected all types of infections, unlike many studies that focus on the occurrence of serious and/or opportunistic infections with infliximab.(5,6,26,27) The definition of disease activity may be questionable as it was only based on subjective clinical scores and did not take into account biomarkers and endoscopic assessment. Disease activity may be a confounder since it was associated with infection and may drive the physician to optimize infliximab but the ΣAUC was associated even stronger with the risk of infection in case of remission. The CRP was not used for that purpose because it is increased by current infection.

In conclusion, high exposure to infliximab increases the risk of infection. There are important implications for patients treated with infliximab. Whereas several recent studies advocate the benefits of infliximab optimization to provide better control of inflammation in IBD,(13,15,28) the potential gain of efficacy should also be weighed against the increased risk of infection. Our findings may

encourage clinicians to consider drug de-escalation when feasible for patients in clinical remission to avoid infections.

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TABLES AND FIGURES LEGENDS

Table 1: Patients' characteristics at baseline

Table 2: Prevalence and type of infections reported by patients treated with infliximab during the study

Table 3: Factors associated with infection over the 6-month period by univariate and multivariate analyses

Figure 1: Comparative concentration-time profiles of infliximab and corresponding cumulated exposure. The upper plot shows the simulated concentration-versus-time curves in a 70-kg patient receiving either 5 mg/kg q6w (full line) or 10 mg/kg q8w (dashed line). The lower plot shows the corresponding cumulative area under the curve (AUC) for each regimen. Note that the Cmin values are equivalent with both regimens, whereas the cumulative exposure is higher with the 10mg/kg q8w regimen.

Figure 2: Flow chart

Figure 3: Association of the 6-month cumulative area under the concentration-time curve of infliximab exposure (ΣAUC) and the risk of infection. The histograms show the association of the mean ΣAUC with the risk of any infection (p=0.04) (**A**) and with the number of infections reported (p=0.04) (**B**).

Supplementary Figure 1: Correlation between several methods of area under the curve (AUC) estimation. **AUC1** according to the Fasanmade 2-compartement model (Fasanmade AA et al, Clin Ther.2011;33:946-64) **AUC2** according to the Buurman 2-compartment model (Buurman DJ, et al. Aliment Pharmacol Ther. 2015;42:529-39) **AUC3** according to the Ternant 1-compartment model **(**Ternant D, et al. *Clin Pharmacokinet* 2018; 57:1173–84). **AUC4 and 5** correspond to homemade 1-compartment model. (Abbreviation: Corr., correlation using the spearman test)

Supplementary Figure 2: Association between infections and trough concentration of infliximab

Supplementary Figure 3: Correlation between the number of infections over the study period and the decile of cumulative area under the curve (cAUC), showing a quantitative link between higher cAUC and the cumulated 6-months number of infections (statistic performed by Poisson regression, p<0,001 for all)

Supplementary Table 1*:* Infliximab treatment regimen variation over the study period

Supplementary Table 2: Biology over the study period

Supplementary Table 3: Factors associated with a high 6-month cumulative area under the curve (AUC) of Infliximab

Supplementary Method: additional description for study population (data) and exposure determination

Table 1 : Patients' characteristics at baseline

		N = 209
Sex (Male / Female) – n (%)	102 (49) / 107 (51)	
Age – mean (±SD)	39 (± 14)	
Type of IBD (CD / UC) – n (%)	159 (76) / 50 (24)	
Duration of IBD (years) – mean (±SD)	12.4 (± 7.7)	
BMI – mean (±SD)	25.0 (± 5.2)	
Smoking (Smokers / Ex-smokers / No-smokers) – n (%)	50 (24) / 40 (19) / 119 (57)	
IBD Phenotype		**N = 209**
A1 ≤ 16 years – n (%)	34 (16)	
A2 ≥ 17 years ≤ 40 years – n (%)	148 (71)	
A3 > 40 years – n (%)	27 (13)	
CD characteristics at the time of inclusion		**N = 159**
B1 inflammatory – n (%)	100 (62)	
B2 stricturing – n (%)	33 (21)	
B3 penetrating – n (%)	26 (16)	
p perianal disease – n (%)	60 (37)	
L1 ileal – n (%)	31 (19)	
L2 colonic – n (%)	38 (24)	
L3 ileocolonic – n (%)	90 (57)	
L4 isolated upper disease – n (%)	20 (13)	
UC characteristics at the time of inclusion		**N = 50**
E1 ulcerative proctitis – n (%)	10 (20)	
E2 left side UC – n (%)	19 (38)	
E3 extensive UC – n (%)	21 (42)	
Prior Surgery		**N = 209**
Previous bowel surgery – n (%)	54 (26)	
Previous perineal surgery – n (%)	50 (24)	
Medical treatment		**N = 209**
IFX duration at inclusion (years) – mean (±SD)	5.0 (± 3.7)	
Combination therapy with IS – n (%)	54 (26)	
- Methotrexate – n (%)	12 (6)	
- Thiopurine – n (%)	42 (20)	

Abbreviations : BMI. Body Mass Index ; CD. Crohn's Disease ; IFX. Infliximab ; IS. Immunosuppressant ; SD. Standard deviation ; UC. Ulcerative Colitis

Table 2 : Prevalence and type of infections reported by patients treated with infliximab during the study

Any infections	
	N=640 infusion visits
≥ 1 Infectious event – n (%)	205 (32)
	N=209 patients
Infections per patient – mean (± SD)	1 (± 1.1)
Patients concerned by infections – n (%)	123 (59)
1 infection	59 (28)
2 infections	39 (19)
3 infections	22 (11)
4 infections	3 (1.4)
Antibiotic therapy	46 (22)
≥ 2 antibiotic therapies	8 (3.8)
	N=215 infections
Bacterial infections – n (%)	63 (29)
Viral infections – n (%)	143 (67)
Fungal infections – n (%)	9 (4.1)
Site of infection – n (%) :	
ENT	122 (57)
Gastrointestinal	26 (12)
Cutaneo-mucosal	26 (12)
Influenza or influenza-like illnesses	18 (8.4)
Urogenital	10 (4.7)
Dental	5 (2.3)
Ophtalmic	5 (2.3)
Pulmonary	3 (1.4)

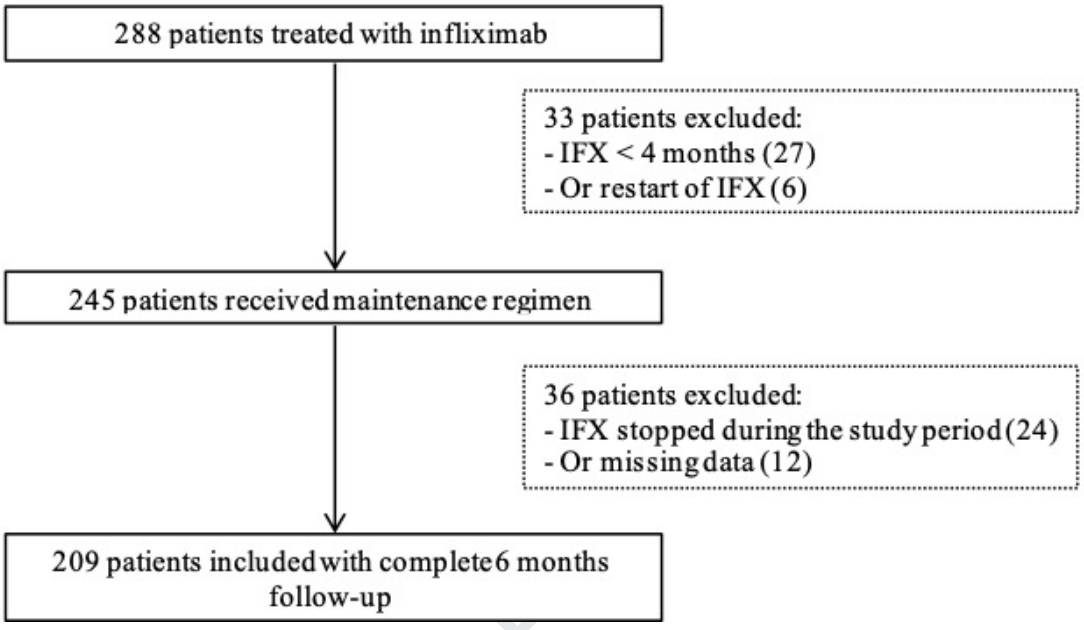
Abbreviations : ENT, otorhinolaryngological

Table 3 : Factors associated with infection over the 6-month period by univariate and multivariate analyses

Covariates	Univariate analysis	Multivariate analysis	
	p value	OR [95% CI]	p value
Sex (Male)	0.57		
BMI	0.77		
Smoker	0.06	2.05 [1.01-4.16]	0.046
IBD Phenotype			
Type of IBD (CD / UC)	0.60		
Montreal A (reference A1)	0.37		
Crohn's Disease			
Montreal B	0.27		
Montreal L	0.80		
Montreal L4	0.45		
Montreal p	0.37		
Ulcerative colitis			
Montreal E	0.53		
Prior Surgery			
Previous bowel surgery	0.33		
Previous perineal surgery	0.24		
Medical treatment			
Duration of IFX therapy	0.28		
Combination therapy with IS	0.8		
Disease Activity (≥ 1 relapse)	0.001	2.71 [1.32-5.54]	0.006
Biology			
Mean albumin concentration	0.75		
ΣAUC for IFX (> 3234 mg.h/L for MA)	0.04	2.02 [1.11-3.65]	0.020

Abbreviations : BMI, Body Mass Index ; CD, Crohn's Disease ; IBD, inflammatory bowel disease ; IFX, Infliximab ; IS, Immunosuppressant ; MA, Multivariate Analysis ; SD, Standard deviation ; TLI, trough concentration of infliximab ; UC, Ulcerative Colitis ; ΣAUC : 6-month cumulative Area Under the Concentration versus time curves

Figure 2 : Flow chart



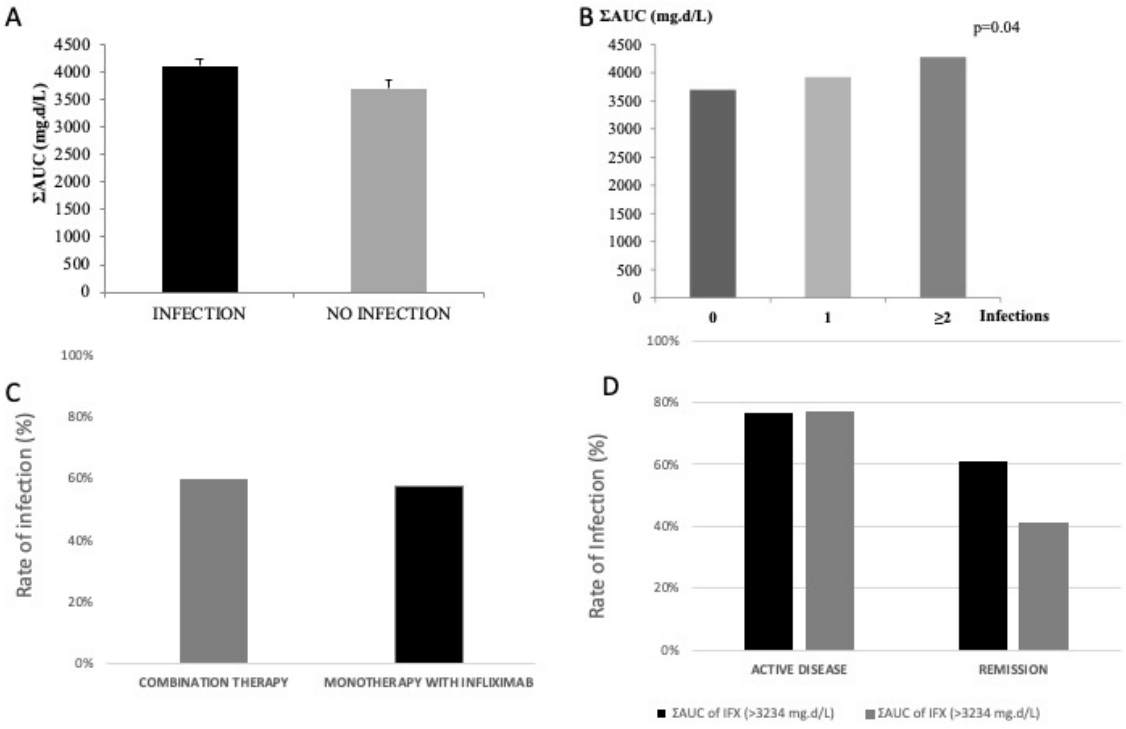
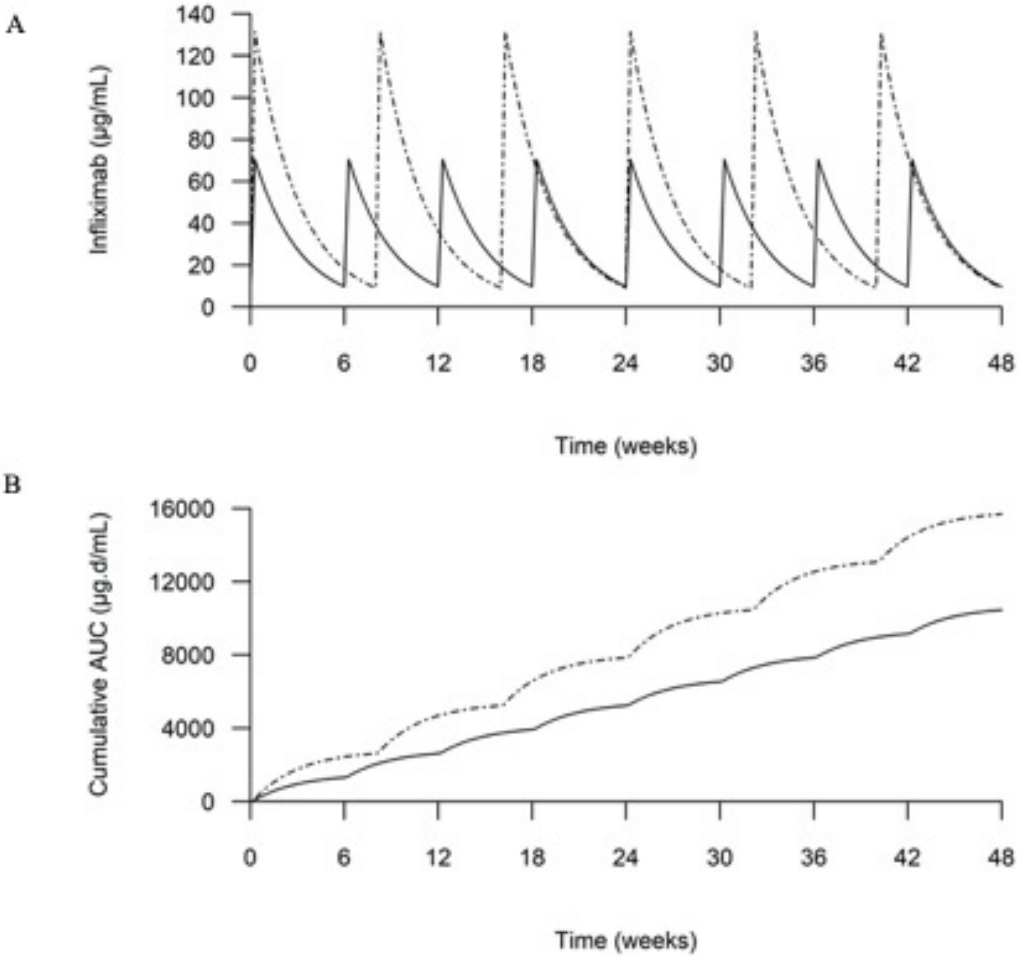
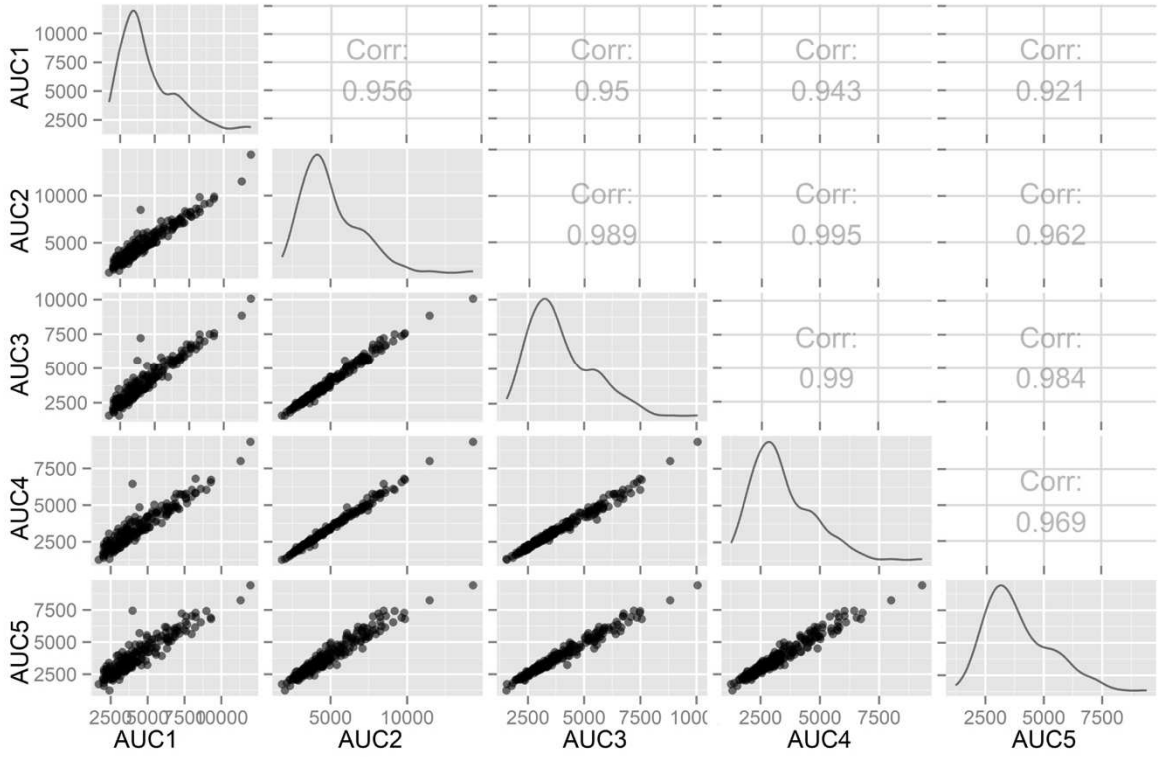


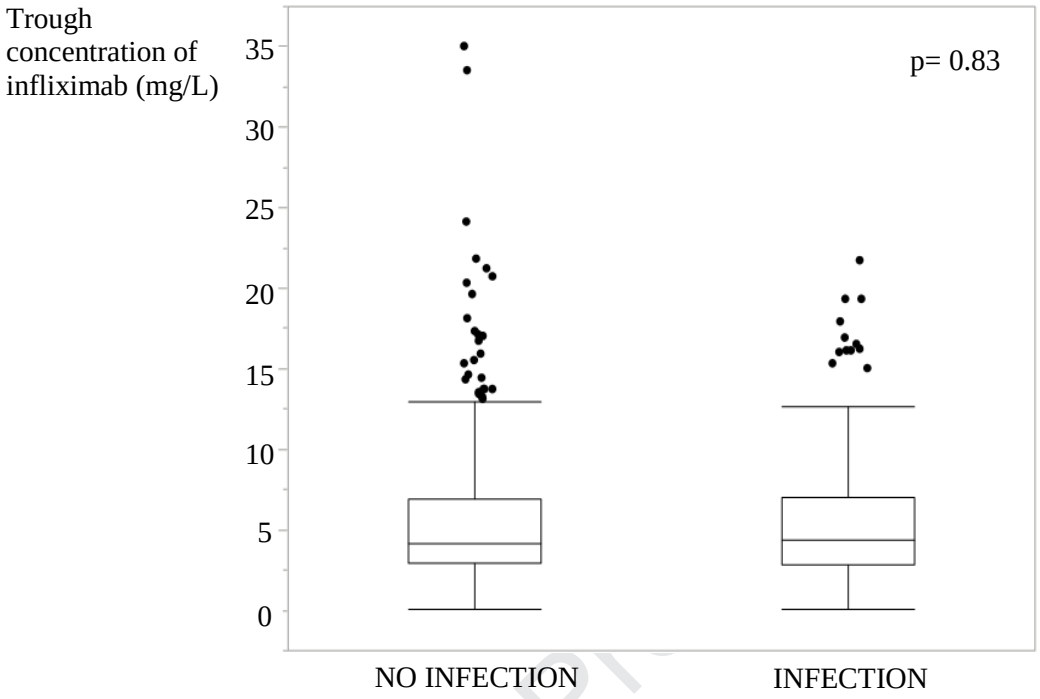
Figure 1: Comparative concentration-time profiles of infliximab and corresponding cumulated exposure. The upper plot (A) shows the simulated concentration-versus-time curves in a 70-kg patient receiving either 5 mg/kg q6w (full line) or 10 mg/kg q8w (dashed line). The lower plot (B) shows the corresponding cumulative AUC for each regimen. Note that the Cmin values are equivalent with both regimens, whereas the cumulative exposure is higher with the 10mg/kg q8w regimen.



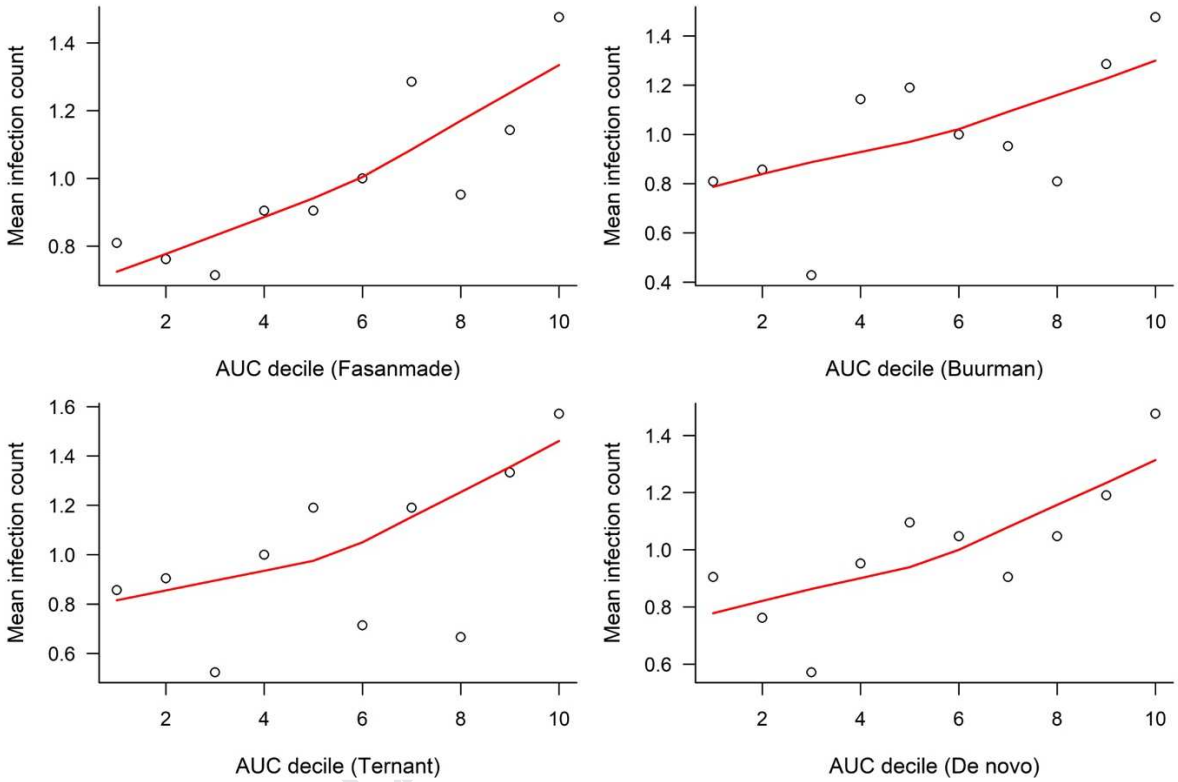
Supplementary Figure 1 : Correlation between several methods of AUC estimation. **AUC1** according to the Fasanmade 2-compartement model (Fasanmade AA et al, Clin Ther.2011;33:946-64) **AUC2** according to the Buurman 2-compartment model (Buurman DJ, et al. Aliment Pharmacol Ther. 2015;42:529-39) **AUC3** according to the Ternant 1-compartment model **(**Ternant D, et al. *Clin Pharmacokinet* 2018; 57:1173–84). **AUC4 and 5** correspond to homemade 1-compartment model. (Abbreviation : Corr., correlation using the spearman test)



Supplementary Figure 2 : Association between infections and trough concentration of infliximab



Supplementary Figure 3: Correlation between the number of infections over the study period and the decile of cumulative area under the curve (cAUC), showing a quantitative link between higher cAUC and the cumulated 6-months number of infections (statistic performed by Poisson regression, p<0,001 for all)



Supplementary Table 1 : Infliximab treatment regimen variation over the study period

Maintenance regimen of Infliximab at baseline - n (%)		
		N=209
Recommended regimen (5 mg/kg every 8 weeks)		**100 (48)**
Alternative regimen		**109 (52)**
5mg/kg	/ less than 8 weeks	21 (10)
	/ more than 8 weeks	42 (20)
7,5 mg/kg	/ 8 weeks	4 (1.9)
10 mg/kg	/ 8 weeks	24 (11)
	/ less than 8 weeks	15 (7.2)
	/ more than 8 weeks	3 (1.4)
Scheme of Infliximab during the follow-up - n (%)		
		N=209
Constant maintenance regimen		**176 (84)**
Intensification		**17 (8.1)**
increased dose		6 (2.9)
increased frequency		11 (5.3)
De-escalation		**16 (7.7)**
decreased dose		9 (4.3)
decreased frequency		6 (2.9)
decreased dose and frequency		1 (0.5)
Disease activity during the follow-up		
		N=209
Steroid use during the study period – n (%)		5 (2.4)
Disease Activity (≥ 1 relapse during the study period) – n (%)		56 (27)

Supplementary Table 2 : Biology over the study period

	N=209
Hemoglobin (g/dl) – mean (± SD)	14.1 (±1.4)
PMNs (UI/mm^3) – mean (± SD)	3936 (±1400)
Lymphocytes (UI/mm^3) – mean (± SD)	2268 (±844)
Platelets (UI/mm^3) – mean (± SD)	287231.5 (±74543)
CRP (mg/L) – mean (± SD)	4.3 (±6.1)
Albumin – mean (± SD)	43.6 (±2.8)
IFX trough concentration (mg/L) – mean (± SD)	5.46 (±4.30)
ΣAUC of IFX (mg.d/L) – mean (± SD)	3938 (±1427)

Abbreviations : AUC : Area Under the concentration versus time Curve ; CRP, C-Reactive protein ; IFX, Infliximab ;PNN, polymorphonuclear neurophils; SD, Standard deviation

Supplementary Table 3 : Factors associated with a high 6-month cumulative AUC of Infliximab

	ΣAUC (mg.d/L)		**p-value**
	< 3234 (n=81)	**> 3234 (n=128)**	
Medical treatment			
IFX duration at inclusion (years) – mean (±SD)	5.72 (3.71)	4.6 (3.6)	0.03
Combination therapy with IS – n (%)	14 (17)	40 (31)	0.02
Dose (mg/kg) – mean (±SD)	5.1 (0.67)	6.5 (2.2)	<0.0001
Intervalle (weeks) – mean (±SD)	8.82 (1.51)	7.9 (1.45)	0.0003
Biology during the study period			
IFX trough concentration (mg/L) – mean (±SD)	3.3 (1.77)	6.6 (3.9)	<0.0001

Abbreviations: IBD, inflammatory bowel disease; IFX, Infliximab; IS, Immunosuppressant; ΣAUC, 6-month cumulative Area Under the concentration versus time Curve; SD, standard deviation

Supplementary Method

Additional information of study population

The following key data were recorded at inclusion: sex, age at diagnosis, height, weight, smoking habits, luminal CD and UC phenotypes according to the Montreal classification (17) at diagnosis, start date for IFX treatment, previous and concomitant medications (including steroids, 5-ASA and immunosuppressants) and surgical history.

During the study period, clinical and biological data were prospectively recorded at each IFX infusion: the dose of IFX received at the last and current visits (mg/kg), the interval between infusions (weeks), the clinical disease activity indices, the occurrence of infections since the last visit infusion and the use of antibiotics, the trough concentration of IFX (mg/L), the haemogram, the C-reactive-protein (CRP, mg/L) and albumin (g/L) concentrations.

additional description of exposure determination

Because of the multiple IFX infusion modalities that exist in a real-world cohort of IBD patients, the same value of TLI can be found in patients with different exposures as assessed by the area under the concentration-time curve (AUC), as illustrated in Figure 1. Therefore, we estimated the actual exposure to IFX over the study period by calculating the cumulated AUC (ΣAUC). A Bayesian estimation of individual pharmacokinetic parameters at each infusion interval was performed using a previously published model.(19) Briefly, this model consisted of a one-compartment compartment model with first order elimination; the estimation of the individual parameters was refined by the use of the relevant individual characteristics that were identified to influence the value of the pharmacokinetic parameters (covariates). The covariate model included the influence of body weight and gender on the value of the clearance. An inter-infusion variability was added to account for the changes in clearance during the observation period. The AUC representing the exposure over an infusion interval was derived from the dose/clearance ratio. This method is particularly convenient when only trough concentrations are available, because the clearance can be reliably estimated from the trough concentration by compartment modelling. Therefore, no measurement other than the trough concentration is necessary to estimate the total clearance and then determine the AUC. The individual pharmacokinetic parameters (clearance and volume of distribution) were estimated by determination of the Empirical Bayes Estimates (EBE) which represent the more probable values of the individual parameters using a Bayesian approach. The ΣAUC over the observation period was obtained by summing the AUCs of all the infusions of the study period in a given individual. Pharmacokinetic modelling was conducted with Monolix 4.3.3. (Lixoft, France). Of note, the 1-compartment model used for AUC calculation may lead to a systematic overestimation of the cAUC, because monoclonal

antibodies are known to follow a 2-compartment model; however, since only trough concentrations were available, the distribution process could not be reliably estimated. Other published models (including 2-compartment models) were tested and were well correlated (Supplementary Figure 1)."

What You Need to Know

Background: Infliximab increases the risk of infection in patients with inflammatory bowel diseases (IBD), but there is controversy over the relationship between drug concentration and infections.

Findings: Almost two-thirds of patients treated with infliximab developed an infection; risk correlated with cumulative increase in drug exposure but not infliximab trough level.

Implications for patient care: Patients who smoke, have IBD flares, or receive high doses of infliximab for treatment of IBD should be carefully monitored for infections.