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Combination of C-reactive Protein, Infliximab Trough Levels, and Stable but Not Transient Antibodies to Infliximab Are Associated With Loss of Response to Infliximab in Inflammatory Bowel Disease

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Abstract

Background: Antibodies to infliximab [ATI] and trough levels to infliximab [TRI] are associated with loss of response in inflammatory bowel diseases [IBD]. The best way to predict loss of response [LOR] to infliximab [IFX] is unknown.

Methods: We conducted a prospective observational cohort study enrolling all IBD patients who were in clinical remission at Week 14 after IFX treatment initiation. TRI, ATI and C-reactive protein [CRP] level were measured at Week 22 [T1] and thereafter at every other IFX infusion. Loss of clinical response was defined by a flare requiring therapeutic change [IFX dose intensification, initiation of another drug class, and/or surgery].

Results: A total of 93 patients [59 Crohn's disease, mean duration of follow-up 17.2 months] were included; 32 patients [34.4%] lost clinical response during follow-up. Cumulative probability of LOR was 50% at 20 months. Mean TRI at T1 was significantly lower in IBD patients with stable ATI as compared with those with transient ATI or without ATI [0.052, 3.34 ,and 4.29 µg/ml, respectively; $p = 0.001$ between no ATI vs stable ATI, and p = 0.005 between stable and transient ATI] [$p = 0.0001$]. Three independent factors were predictive of LOR after Cox proportional hazards modelling: TRI > 5.5 µg/ml (hazard ratio [HR]: 0.21; 95% confidence interval [CI]: 0.05–0.89;$p = 0.034$) at T1, CRP > 5mg/l [HR: 2.5; 95% CI: 1.16–5.26; $p = 0.019$] at T1, and stable ATI defined by two consecutive ATI > 20ng/ml [HR: 3.77; 95% CI: 1.45–10.0; $p = 0.007$]. Transient ATI did not influence LOR.

Conclusions: LOR can be predicted based on a combination of CRP, TRI and stable ATI with a high degree of accuracy.

Keywords: Infliximab; antibodies to infliximab; kinetics; loss of response; Crohn's disease; ulcerative colitis; inflammatory bowel disease

1. Introduction

Anti-tumour necrosis factor [TNF] is increasingly used to treat inflammatory bowel disease [IBD] refractory to standard medications. However, loss of response [LOR] is frequent with all anti-TNF agents.[1,2] Two meta-analyses demonstrated that antibodies to infliximab [IFX] and adalimumab are associated with LOR in IBD.[3,4] Hence, there is a growing interest in measuring ATI in clinical practice in order to optimise disease outcomes among anti-TNF treated patients with IBD.

Importantly, measuring ATI at a given moment in time is not sufficient, as ATI may be transient. For the first time, Steenholdt *et al*. described transient ATI and their clinical implication.[5] Moreover, in an elegant retrospective study from the Leuven group, the authors showed for the first time that ATI may be transient and do not always lead to a worse clinical outcome. By contrast, sustained high levels of ATI lead to permanent LOR.[6]

However, they used a qualitative approach to define positivity of ATI and did not investigate the optimal cut-off of permanent ATI to predict LOR. Also, they could not formally evaluate the duration of ATI response as it was a retrospective study with no systematic testing of all IBD patients at scheduled times. In this landmark study,[6] ATI and TRI were measured using a novel Homogeneous Mobility Shift Assay [HMSA]. Recently, Steenholdt *et al*. compared four commonly used techniques for measuring TRI and ATI.[7] Circulating ATI activity reported by gene assay [RGA] was absent in 68% of serum samples testing positive for ATI by HMSA, indicating that ATI reported by HMSA may have little or no drug-neutralising effect or may detect false-positive testing of non-functional ATI. Importantly, ATI detection by RGA and byenzyme-linked immunosorbent assay [ELISA] was broadly similar. This is the reason why we choose in our study to measure ATI with an ELISA test. More recently, in a prospective study, most patients who developed ATI did so within the first 12 months of therapy.[8] It was found that transient ATI can appear at any time during anti-TNF treatment.[8]

Therefore, the aims of our prospective observational cohort study were to investigate the combined effect of CRP, TRI, and permanent ATI for predicting LOR among IBD patients treated with IFX.

2. Methods

2.1. Study design

We conducted a prospective cohort study of all consecutive adult IBD patients treated with IFX in the Gastroenterology Department of Saint-Etienne University Hospital, France, between September 2010 and February 2012 [Figure 1].

All consecutive adult patients with an established diagnosis of CD or UC and in clinical steroid-free remission, defined by a Crohn's Disease Activity Index [CDAI] calculated prospectively for all patients at each visit and scoring below 150 for CD,or a partial Mayo score below 3 for UC under IFX treatment [5 mg/kg] at Week 14 and Week 22, were eligible for inclusion in our study. All patients were included in the study at Week 22 [T1] after IFX treatment initiation and were followed for at least 6 months after taking the second sample at Week 38. Our study protocol was approved by our local committee and all included patients signed a written consent. We measured also TRI and ATI for 80% of our patients at Week 14 [T0]. We were blinded to these results until the end of follow-up.

Exclusion criteria were: patient's refusal to enter the study, age under 18 years, indeterminate colitis, only one measurement of TRI and ATI, a follow-up below 6 months and primary non-responders. All included patients were naïve to anti-TNF therapy at time of IFX treatment initiation and received scheduled induction therapy with 5 mg/kg IFX infusion at Weeks 0, 2, and 6 and thereafter maintenance therapy every 8 weeks. Each IFX infusion was preceded by premedication with intravenous hydrocortisone 200 mg according to routine practice in our department. Serum samples were prospectively collected just before IFX infusion starting at Week 22 [T1] and thereafter every 2 IFX infusions during maintenance therapy, or more frequently if needed [T2]. They were collected and analysed blindly to clinical data and stored at -20°C. C-reactive protein [CRP] level was also measured at every IFX infusion.

At every serum sample taken to measure TRI and ATI, IFX dose [5 mg/kg or 10 mg/kg], clinical activity using CDAI for CD or partial Mayo score for UC, CRP levels, and concomitant medications were collected.

Clinical remission was defined as a CDAI < 150 or a partial Mayo score < 3 without steroid treatment. Loss of clinical response to IFX [LOR] was defined as an increase in symptoms [CDAI > 220

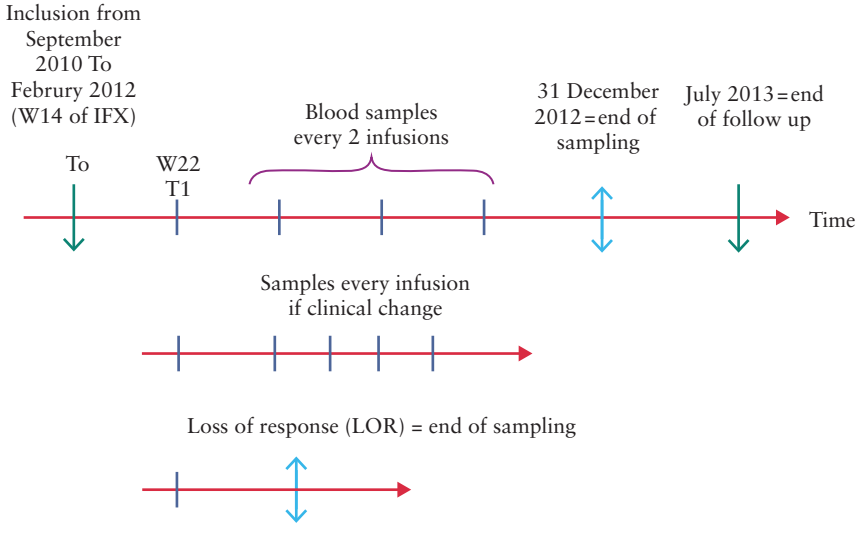

Figure 1. Overview of the study protocol.

or partial Mayo score > 5] requiring a change in therapy including steroids initiation or a need for surgery, blindly to therapeutic drug monitoring of IFX.

2.2. TRI, ATI and CRP measurements

IFX and ATI concentrations were measured using the Lisa-Tracker Premium Infliximab ELISA kit [Theradiag, France]. This assay has been developed to reduce low affinity binding of immune complexes or interfering molecules such as the rheumatoid factor. The use of specific buffers for both binding and washing steps allows a very efficient capture of free molecules. IFX was considered undetectable at a concentration < 0.1 µg/ml. The ATI detection level reported by the manufacturer was > 10 ng/ml. In IBD patients with undetectable ATI, ATI were also measured with another technique recently published and described to detect high frequency of ATIs [27.6%].[9] ATI were defined as positive with this cut-off. Positive ATI frequency was defined as a percentage of positivity in all samples. Transitory ATI was defined for IBD patients by presence of only one positive ATI or by ATI positivity followed by ATI negativity and then followed by a new ATI positivity. Stable ATI was defined by at least two consecutive positive ATI. CRP levels were measured using an ultrasensitive assay [Roche Diagnostics].

2.3. Statistical analysis

Continuous variables were expressed as mean and standard deviation [SD], and categorical variables were expressed as percentages. The χ^2 test and the Mann–Whitney test were used to compare categorical and quantitative variables. When considering TRI and ATI at T1, a receiver operating characteristic [ROC] curve analysis was performed using clinical remission as a classification variable to calculate the sensitivity [Se], specificity [Sp], likelihood ratio [LHR], and area under the ROC curve [AUROC] with the associated *p*-value. Se, Sp, LHR, and AUROC were determined for clinical remission in the follow-up. Survival analysis used the Kaplan–Meier method to assess the cumulative incidence of LOR. The univariate analysis of overall survival was performed by using the method of Kaplan–Meier. Curves were compared by the log-rank test. To identify independent predictors of survival without LOR during follow-up, variables that achieved a $p < 0.1$ were included in a multivariate analysis by using a proportional hazards Cox regression procedure. All reported *p*-values were 2-sided, and $p < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS 20.0.0 [IBM, Somers, NY].

3. Results

Between September 2010 and December 2012, 93 IBD patients treated with IFX and in clinical remission at Week 14 and Week 22 [T0 and T1] were included: 59 CD [63%], median age at diagnosis 27 [21–40], sex ratio male/female of 1.2, median disease duration before start IFX of 5.8 [2.6–12.6] years. Characteristics of included patients are reported in Table 1. After Week 22 [T1], 481 serum samples were collected during follow-up, with an average number of samples per patient of 5.2.The median duration between inclusion and end of follow-up was 20 [11.1–22.9] months. A total of 27 patients [29%] were receiving concomitant thiopurine therapy at the time of the first sample [T1] [35% of CD patients and 20% of UC patients]; 27 patients [29%] had a CRP > 5 mg/l at T1, and 25 of these patients had a CRP > 5 mg/l at T0 with comparable levels between the two times. Only two patients had increased CRP levels between T0 and T1 without clinical activity. The median CRP levels in patients without LOR was 3.5 mg/l and 12.5 mg/l during relapse.

Table 1. Baseline characteristics.

	Median
Sex ratio male/female	1.2
Median age at diagnosis [years] [IQR]	30 [21–40]
Crohn's disease, *n* [%]	59 [63]
Terminal ileum = L1	19 [32]
Colon = L2	16 [27]
Ileocolon = L3	23 [39]
Non-stricturing, non-penetrating = B1	26 [44]
Stricturing = B2	25 [42]
Penetrating = B3	11 [19]
Perianal disease suppress = p	22 [37]
Ulcerative colitis, *n* [%]	34 [37]
Proctitis = E1	3 [9]
Left-sided = E2	12 [35]
Extensive = E3	19 [56]
Median disease duration before start IFX [years] [IQR]	5.8 [2.6–12.6]
Median follow-up duration [months] [SD]	20.2 [11.1–22.9]
Concomitant thiopurine at T1, *n* [%]	27 [29]
Average number of serum samples per patient [SD]	5.2 [2.6]
Patients with CRP > 5 mg/l at T1, *n* [%]	27 [29]

IFX, infliximab; T1, time of the first sample; CRP, C-reactive protein; IQR, interquartile range.

3.1. Clinical remission at last known follow-up

During follow-up, 32 patients [34.4%] lost response to IFX. IFX therapy was intensified in 10 patients, therapy was changed in 14 patients, surgery was required in 7 patients, and no change of IFX but initiation of steroids *was* performed in one patient [Supplementary Figure 1, available as Supplementary data at *ECCO-JCC* online]. Clinical remission was observed in 61 patients [65.6%], with 59 patients being still under IFX therapy. One patient had an infusion reaction to IFX [with ATI above 200 ng/ml], and one patient developed a disabling psoriasis related to IFX [with IFX above 7 µg/ml]. These two patients were switched to adalimumab therapy and were in clinical remission at last news. They were considered to be in loss of response under IFX in this study.

3.2. Kinetics of antibodies to infliximab and infliximab trough levels

Characteristics of patients with and without stable ATI are reported in Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online. Only TRI were significantly lower at T1 in patients with stable ATI [0.0526 µg/ml vs 4.24 µg/ml; $p < 0.001$]. Characteristics of patients with no ATI [$N = 66$] and transient ATI [$N = 18$] were similar [data not shown]. Initial levels of ATI were lower in transient ATI than in patients were stable ATI, but it did not reach statistical significance [12 ng/ml vs 28 ng/ml, $p = 0.08$]. We performed a ROC analysis for prediction of stable ATI and it was not significant [AUROC: 0.59; $p = 0.055$]. Of the 66 patients without positive ATI, 45 [68%] were still responding to IFX at last follow-up. Of the 14 patients with 1–49% samples positive for ATI, only 2 [14%] lost response during follow-up, whereas of the 8 patients with 50–99% samples positive for ATI, 4 [50%] lost response. All 5 patients with all samples positive for ATI experienced LOR during follow-up [$p = 0.0044$] [Supplementary Figure 2, available as Supplementary data at *ECCO-JCC* online].

Concomitant thiopurine treatment was not associated with ATI formation neither with time to development of ATI. The median time to development of the first positive ATI after IFX treatment initiation was 14.6 [8.6–20.6] months with and 32.3 [20.2–66.3] months without concomitant thiopurine treatment [p = non-significant]. There was no difference regarding duration of IFX therapy for transient vs stable ATI. In addition, the use of concomitant thiopurines did not influence the rate of transient or stable ATI.

Mean TRI at T1 was lower in IBD patients with stable ATI as compared with those with transient ATI or without ATI [0.052, 3.34, and 4.29 µg/ml, respectively; p = 0.001 between no ATI vs stable ATI, and p = 0.005 between stable and transient ATI] [Figure 2A]. There was a decrease in median TRI between patients measured at T0 [Week 14], those measured at T1, and patients evaluated at T2 [Week 30] [4.28 vs 2.34 vs 1.61 µg/ml, respectively] [Figure 2B] [p = 0.03 between T0 and T1, and p = 0.03 between T1 and T2].

At T1, and when pooling on all samples taken at any time during follow-up, there was an inverse correlation between TRI and ATI (Spearman coefficient r = [-0.3376], p < 0.001; r = [-0.3338], p < 0.001, respectively). There was no correlation between duration of IFX therapy and ATI levels [Spearman coefficient r = 0.0041, p = 0.69]. TRI at T1 was better correlated with ATI level at T2 [Supplementary Table 2, available as Supplementary data at *ECCO-JCC* online].

3.3. Cumulative incidence of LOR

The cumulative incidence of LOR was 14% at 6 months, 28% at 12 months, 40% at 24 months, and 80% at 32 months after study inclusion [e.g. Week 22 after the first infusion of IFX]. The cumulative incidence of LOR by year was 14% the first year after IFX treatment initiation, 22% for the second year, and 29% the third year [Figure 3].

3.4. Associated factors to LOR

We performed a ROC analysis to research the best cut-off value of TRI at T1 for prediction of LOR in the follow-up [AUROC = 0.768; p < 0.001]. Cut-off of TRI < 5.5 µg/ml was the best threshold value to predict LOR [sensitivity: 24.6%; specificity: 83.9%; LHR: 7.7] [Supplementary Figure 3, available as Supplementary data at *ECCO-JCC* online]. The results of univariate analysis [log-rank test] are presented in Table 2. Five factors were associated with LOR:

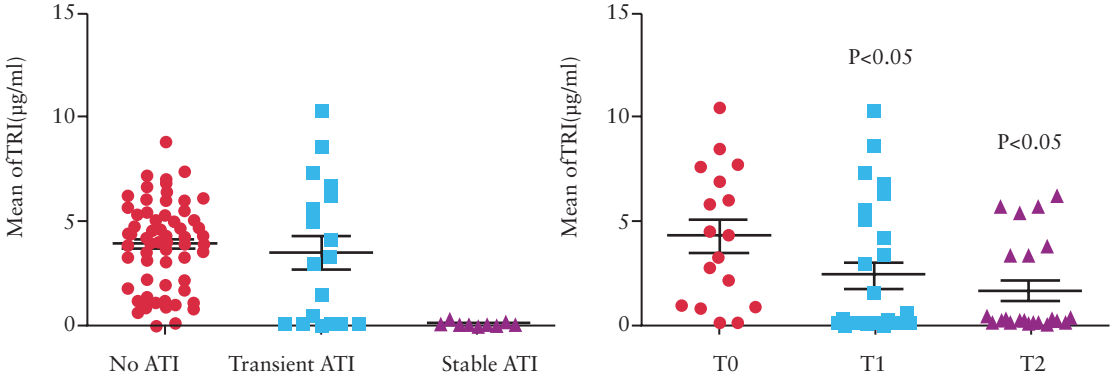

Figure 2. [A]TRI according to ATI status; and [B] kinetics ofTRI over time.

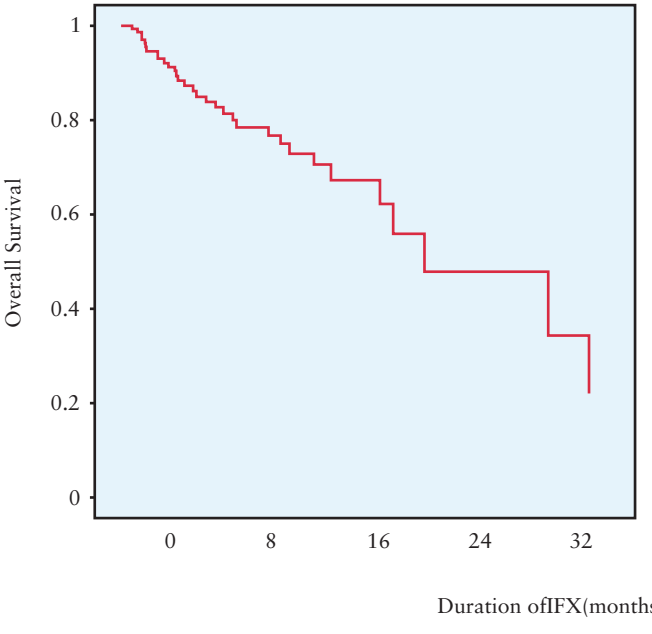

Figure 3. Cumulative incidence of loss of response [LOR].

Table 2. Univariate analysis of factors associated with LOR during the follow-up at T1.

Variables	Log-rank test
Stable vs no or transient ATI	0.01
Transient vs no ATI	0.09
ATI > 20 ng/ml vs < 20 ng/ml	0.01
TRI < 5.5 µ/ml vs > 5.5 µg/ml	<0.01
CRP> 5 mg/l vs <5 mg/ml	<0.01
IS vs ni IS associated	0.2

ATI, antibodies to infliximab; CRP, C-reactive protein; IFX, infliximab; IS, Immunosuppressive drugs.

Table 3. Independent predictors of LOR [loss of response] using Cox proportional hazards modelling.

Predictor of LOR	Hazard ratio	95% CI	*p*
Stable ATI	3.77	1.45–10	0.007
CRP > 5 mg/l at T1	2.5	1.16–5.26	0.019
TRI > 5.5 µg/ml at T1	0.21	0.05–0.89	0.034

ATI, antibodies to infliximab; CRP, C-reactive protein; TRI, trough levels to infliximab; T1, time 1.

stable ATI [Supplementary Figure 4A, available as Supplementary data at *ECCO-JCC* online], ATI > 20ng/ml at T1 [Supplementary Figure 4B], TRI at T1 > 5.5 µg/ml [Supplementary Figure 5, available as Supplementary data at *ECCO-JCC* online], and CRP > 5 mg/l [Supplementary Figure 6, available as Supplementary data at *ECCO-JCC* online]. Concomitant thioprine treatment at T1 [Supplementary Figure 7, available as Supplementary data at *ECCO-JCC* online] and transient ATI were not associated with LOR [$p = 0.2$ and $p = 0.09$, respectively]

We next performed a Cox proportional hazards modelling including four parameters: CRP, TRI, ATI levels, and stable ATI [Table 3]: stable ATI [HR: 3.77; 95% CI: 1.45–10.0: $p = 0.007$], CRP > 5mg/l [HR: 2.5; 95% CI: 1.16–5.26; $p = 0.019$], and TRI > 5.5 µg/ml [HR: 0.21; 95% CI: 0.05–0.89: $p = 0.034$] were independent predictors of LOR.

The percentage of patients in clinical remission at last known follow-up was 93% if CRP was < 5mg /l and TRI was > 5.5 µg/ml at T1. The percentage of patients in clinical remission at last known follow-up was only 40% if CRP was < 5 mg/l, TRI < 5.5 µg/ml at T1 with stable ATI at T2. This percentage was comparable [45%] for patients with CRP > 5mg/l and TRI > 5.5 µg/ml.

4. Discussion

The combination of serum markers, including pharmacokinetics, having the best value to predict LOR to IFX in IBD has yet to be determined. In a study enrolling 84 CD patients, TRI > 3 µg/ml at the start of IFX maintenance regimen was predictive of sustained response to IFX, ATI, and CRP were not predictive of LOR.[10] In a retrospective study, high TRI [>5 mg/ml] at the time of immunomodulator withdrawal was associated with a decreased risk for LOR [HR: 0.16; 95% CI: 0.03–0.74; $p = 0.02$].[9] CRP > 5 mg/l at the time of immunomodulator withdrawal was associated with discontinuation of infliximab because of loss of response [HR: 7.99;95% CI: 2.19–29.25; p = 0.002].[10] In a pilot observational study, proactive therapeutic concentration monitoring of IFX frequently identified patients with low or undetectable trough concentrations and resulted in a greater probability of remaining on IFX.[11] The probability of remaining on IFX was greatest for patients who achieved TRI > 5 µg/ml [HR: 0.03; 95% CI: 0.01–0.1; $p = 0.0001$ vs trough < 5 µg/ml].

The pejorative role of ATI in patients treated with anti-TNF is now well established. In a recent meta-analysis, the presence of ATIs was associated with a significantly higher risk of LOR to IFX and lower serum IFX levels in patients with IBD.[3] There is a growing interest in looking at the impact kinetics of ATI on disease outcomes in IBD.[6,8]

In our study, we first confirmed that stable ATI defined by at least two consecutive positive ATI were associated with LOR, whereas transient ATI had no impact on LOR rates. In a recent retrospective study, Vande Casteele *et al*. empirically defined transient vs sustained ATI when ATI disappeared over time, after a median of 17 weeks vs 45 weeks;[6] patients with transient ATI using an HMSA technique[12] were less likely to discontinue IFX for LOR or hypersensitivity reactions compared with patients with sustained ATI.[6] In this study, the authors empirically defined three groups of patients: no ATI [33 patients], low ATI [< 8 U/ml: 28 patients] and high ATI [> 8 U/ml: 29 patients].

Importantly, we showed that two consecutive positive ATI levels were strongly and independently associated with LOR. This definition could be used in clinical practice to guide decision making. In a prospective observational study of IFX-treated patients with IBD, Ungar *et al*. reported that most patients [46%] who developed permanent ATI did so within the first 12 months of therapy [90%].[8] The median time of ATI was 1.5 months.[8] Transient ATI were detected throughout the duration of infliximab therapy.[8] Transient and permanent ATI were defined a priori as measurable ATI on up to two consecutive infusions without any alteration of therapy.[8] Our definition [stable ATI] may be more clinically relevant, as permanent ATI were defined by at least two consecutive positive ATI. Moreover, we did not include primary non-responders, as only patients in clinical remission at Week 14 were enrolled in our study, whereas Ungar *et al*. measured ATI at Week 2, thus partly explaining discrepancy between our findings and Ungar's study results. Indeed, when evaluating the impact of ATI on LOR, only primary responders to anti-TNF therapy should be analysed.

Interestingly, we showed for the first time that patients [$n = 5$] with stable ATI [using our definition] had a 100% probability of LOR, those with more than 50% of positive ATI had 50% LOR, whereas 86% of patients with only few samples positive for ATI [< 50%] were in clinical remission. It is noteworthy that 68% of IBD patients without ATI were in clinical remission, which is broadly similar to what was observed in those with transient ATI. The threshold of ATI predictive of LOR in our study was lower than previously reported[6] [20 ng/ml vs 8 ng/ml], likely due to the use of different assays.[6] We could not confirm that lower initial ATI levels are more likely to be transient compared to higher initial ATI levels as previously described.[6] However, we did not systematically measure ATI before study inclusion, e.g. before Week 22.

Finally, we found that the TRI used in combination with CRP level had a high value for predicting LOR in these patients. These two variables were independent factors to predict LOR. The cut-off value of TRI isolated in our study is in line with previous studies.[13] At the time of immunomodulator withdrawal, trough levels of infliximab and C-reactive protein were strongly associated with sustained response to infliximab. Moreover, when patients had TRI higher than 5 µg/ml, no relapse was reported during follow-up. Similar to previous reports, the type of IBD did not influence our results.[6]

Two previous reports clearly showed that concomitant immunomodulator use decreases the risk of permanent ATI formation.[6,14,15] In our study, the use of concomitant IS was not associated with better outcome, likely due to small sample sise when looking at the subgroup of patients on combination. Indeed the use of combination therapy was low [29%].

In our study, median TRI have declined in all included patients due to results in the subgroup of patients with stable ATI. Indeed, we report an inverse correlation between TRI and ATI at the time of the first sample and on all samples. For the first time, we showed that TRI are significantly lower in patients with stable ATI and that the decrease in IFX trough level precedes the development of ATI. TRI below 5.5 µg/ml cannot prevent ATI formation. Vande Casteele *et al*. investigated the influence of ATI formation on the kinetics of TRI.[6] In multivariate analysis, we found that TRI > 5.5 µg/ml predicted clinical response under IFX therapy. These findings are similar to those of the Leuven group[6] and are complementary to data coming from a *post hoc* analysis of the ACCENT 1 trial in which TRI > 3.5µg/ml at Week 14 predicted sustained response.[16]

Our study has several strengths. Notably, this was a prospective study with a standardised follow-up and systematic measurement of both ATI and TRI. The measurement of ATI and TRI was performed using the Lisa-Tracker Premium Infliximab ELISA kit [Theradiag], which has been developed to reduce low affinity binding of immune complexes or interfering molecules such as the rheumatoid factor. The use of specific buffers for both binding and washing steps allows a very efficient capture of free molecules. In a recently published study comparing three ELISA methods, there was a good correlation of IFX and ATI measurements between those assays.[17] In addition, in case of undetectable ATI, we used a new immunoassay for the accurate determination of anti-infliximab antibodies in inflammatory bowel disease to decrease false-negative results due to detectable TRI.[9] We know, however, that an ELISA assay has some limitations in detecting ATI in the presence of infliximab excess, but we wanted to know if this technique of measurement could report stable antibodies and if these ATI were associated with poor outcomes. No data were reported with this ELISA test. The notion of permanent antibodies associated with poor outcomes was affirmed with radioimmunoassay,[6] with HMSA,[7] and finally with a modified ELISA using for ATI measurement an antihuman λ chain.[8] So, for the first time, we report that stable ATI were associated with loss of response in the follow-up.

The study has also some limitations such as the relatively small sample size and no differentiation between CD and UC, even though IBD types did not influence our results in multivariate analysis. Also, we did not measure TRI and ATI before Week 22 for all patients. Recent reports indicate that ATI can be detected already 16 to 18 days after the start of IFX therapy.[8] In this study, each IFX infusion was preceded by premedication with intravenous hydrocortisone 200 mg, according to routine practice in our department. There is very little evidence[18] that this approach is beneficial in reducing the risk of development of ATI.

We propose a new algorithm based on TRI, CRP, and permanent ATI for use in clinical practice. In patients with TRI > 5.5 µg/ml and CRP > 5mg/l, the probability of LOR was 45%. So, in these cases, it should be interesting to discuss another drug class.[21] Conversely, in patients with TRI > 5.5 µg/ml and low CRP < 5mg/l, the probability of LOR is very low and does not require treatment modification. Finally, in IBD patients with TRI < 5.5 µg/ml and CRP > 5mg/l, measurement of ATI must be performed; and, in cases of stable ATI, the risk of developing LOR is very high. In these cases, switch to another anti-TNF,[6,19] or addition of an immunomodulator should be discussed.[15] Indeed, in a restrospective study, Ben Horin *et al*. reported that addition of an immunomodulator to infliximab therapy eliminates ATI in serum and restores clinical response of patients with inflammatory bowel disease.[15] Conversely, in patients with no stable ATI and with low TRI and CRP > 5 mg/l, IFX optimisation should be discussed.[6,19] Prospective interventional studies are needed to confirm this suggested algorithm.

Moreover, our data indicating that IFX decreases before ATI formation warrant the initiation of interventional studies to prevent ATI formation and therefore to decrease the subsequent risk of IFX treatment failure.

In conclusion, our findings further underscore the need to take into account both TRI and ATI when managing IFX-treated IBD patients. We propose IFX dose intensification or adding an immunosuppressive drug earlier if TRI is lower that our cut-off value to prevent ATI formation. Conversely, CRP < 5 mg/l and high TRI at Week 22 are strongly predictive of sustained clinical response to IFX. In patients with stable ATI defined by two consecutive samples, the probability of LOR was high during follow-up. CRP was also an independent predictor of LOR. Our data indicating that IFX decreases before ATI formation warrant the initiation of interventional studies to prevent ATI formation and therefore to decrease the subsequent risk of IFX treatment failure.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

Specific author contributions

The whole study was conceived and designed by XR, ML,SP. Statistical analysis was performed by HM. All authors [SP, EDT, HM, MR, ML, LC, JMP, GB, LPB, and XR] were involved in the interpretation of results and discussion. SP, LPB, and XR drafted the manuscript, which was critically revised by all the authors [SP, EDT, HM, MR, ML, LC, JMP, GB LPB, and XR]. All authors also approved the final version of the manuscript.

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Conflict of Interest

For SP, EDT, HM, MR, AM, LC, GB, JMP: no conflict of interest; LPB, lecture and consulting fees from Merck; XR, lecture and consulting fees from Merck and Theradiag.http://ecco-jcc.oxfordjournals.org/lookup/suppl/doi:10.1093/ecco-jcc/jjv061/-/DC1.

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