

Dynamics of serum concentrations of antibodies to infliximab: a new approach for predicting secondary loss of response in inflammatory bowel diseases

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Ther Adv Gastroenterol

2021, Vol. 14: 1–14

DOI: 10.1177/
17562848211037849

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Abstract

Background: Antibodies to infliximab (ATI) in serum are associated with secondary loss of response (LOR) to infliximab (IFX) therapy in patients with inflammatory bowel disease (IBD). However, feasible ATI-related predictors of therapy success are lacking and knowledge about individual ATI dynamics is limited. Therefore, this study analyzed whether ATI dynamics are able to predict LOR to IFX therapy and compared their predictive power with known predictors of LOR to IFX.

Methods: This was a retrospective study of patients with Crohn's disease (CD) or ulcerative colitis (UC) on IFX maintenance therapy and proactive IFX and immunogenicity monitoring in an outpatient clinic in Germany. Slopes of ATI (S_{ATI}) and IFX levels (dynamic parameters) and medians of ATI, IFX, C-reactive protein, and fecal calprotectin (static parameters) were calculated over a defined period of time after ATI emergence. Dynamic and static parameters were analyzed for associations with end points infliximab discontinuation due to secondary LOR and total IFX discontinuation.

Results: In all, 500 visits from 38 IBD patients (28 CD, 10 UC) with a median IFX maintenance duration of 68.2 weeks were evaluated. Grouping by S_{ATI} (ATI-N=ATI nondetectable, ATI- \downarrow =negative S_{ATI} , ATI- \uparrow =positive S_{ATI}) yielded significant differences for outcomes LOR ($p=0.004$) and total IFX discontinuation ($p=0.01$). Patients in the ATI- \downarrow group survived significantly longer LOR-free compared with the ATI- \uparrow group ($p=0.02$). Cox regression confirmed S_{ATI} to be a significant risk factor for LOR ($p=0.002$). An S_{ATI} cut-off of approximately $2.0 \text{ AU mL}^{-1} \text{ week}^{-1}$ was determined to predict LOR with 83.3% sensitivity and 93.8% specificity.

Conclusion: The ATI slope-based index S_{ATI} is a new feasible diagnostic predictor of LOR in IBD patients. S_{ATI} may facilitate quick therapeutic decisions after ATI emerge.

Keywords: antibodies to infliximab, antibody dynamics, Crohn's disease, immunogenicity testing, inflammatory bowel disease, infliximab, personalized medicine, secondary loss of response, therapeutic drug monitoring, treatment failure, ulcerative colitis

Received: 28 April 2021; revised manuscript accepted: 19 July 2021.

Introduction

Biologic antagonists to tumor necrosis factor (TNF) have evolved into a major cornerstone in the management of inflammatory bowel diseases (IBD), that is, Crohn's disease (CD) and ulcerative colitis (UC). TNF antagonists are considered as

disease-modifying drugs and constitute powerful tools to achieve clinical and endoscopic remission.¹ After initial approval, TNF antagonists were indicated as penultimate measure before surgery within the step-care approach. Nowadays, the use of TNF antagonists has shifted toward early intervention.^{2–4}

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The chimeric, monoclonal antibody infliximab (IFX), sold under originator trade name Remicade[®], was the pioneering TNF antagonist to receive Food and Drug Administration (FDA) approval for CD therapy in 1998. In the meantime, IFX biosimilars (e.g. Remsima[®], Inflectra[®]) have entered the market. They are equally effective and safe, but cheaper and hence make IFX accessible for more patients in more countries.^{5,6} Although other TNF antagonists and more gut-specific biologics have been introduced since, IFX is still widely prescribed due to the longtime clinical experience and extensive safety profile available.

The efficacy of IFX, however, is impaired by the capability of biologic drugs to elicit immunogenic reactions: anti-drug antibodies may be generated, leading to enhanced drug clearance, direct neutralization of TNF-binding capacities, and adverse reactions (AR) up to anaphylactic reactions.⁷ Even if known for decades, antibodies to infliximab (ATI) still constitute a major cause for secondary loss of response (LOR) to IFX therapy, which is observed in about one-third of patients.⁸ The resulting inefficient use of the expensive drug places a high economic burden on healthcare systems. Nevertheless, no generally accepted consensus on the details of diagnostics and the optimal therapeutic strategy to manage emerging ATI has been established. Although some large cohort studies, such as the TAXIT (The Trough Concentration Adapted Infliximab Treatment) study, resulted in widely accepted recommendations and therapeutic algorithms, no official consensus on the details of diagnostics and the optimal therapeutic strategy to manage emerging ATI has been established.^{9,10}

It is commonly accepted that IFX serum trough levels between 3 and 8 $\mu\text{g}\cdot\text{mL}^{-1}$ are associated with favorable clinical outcome and reduced rates of secondary LOR.^{1,9} To maintain these levels, proactive therapeutic drug monitoring (TDM) combined with immunogenicity testing (IT), enabling early intervention, may be more effective than mere reactive monitoring triggered by relapse or LOR. However, a final proof of this hypothesis will require supporting results from further prospective studies.^{11,12} Beneficial therapeutic interventions include higher IFX dosages, shorter infusion intervals, or, to prevent ATI formation, additional therapy with immunomodulators, such as azathioprine, to restore high IFX trough levels.^{9,13,14} Evidence suggests that high and permanent ATI in serum are correlated with

worse outcomes than low and transient ATI levels.^{15–18} However, consensus definitions of ‘high’ *versus* ‘low’ or ‘transient’ *versus* ‘permanent’ are lacking and studies on the detailed dynamics of ATI in individual patients are limited. Furthermore, analysis of ATI titers with respect to ‘static’ thresholds is frequently unable to explain or precisely predict clinical outcomes. Individual dynamics of ATI here may offer more valuable information for the clinician.

We therefore analyzed whether ATI dynamics monitored in a defined period of time are able to predict (secondary) LOR to IFX therapy. We furthermore investigated how the performance of ATI dynamics compares with known predictors of LOR, such as ‘static’ ATI titers, IFX trough levels, and inflammation markers. To do so, a real-world cohort of IBD patients on IFX maintenance therapy from a gastroenterologic outpatient clinic with a proactive TDM/IT policy was evaluated retrospectively. In the context of this study, TDM/IT denotes parallel serum IFX trough level determinations and ATI quantification. We suggest the new diagnostic index S_{ATI} , which is indicative of ATI dynamics and was found to be an early predictor of secondary LOR.

Patients and methods

Patients

A total of 41 consecutive patients treated between April 2016 and March 2020 in a specialized gastroenterologic outpatient clinic (Gastroenterologische Gemeinschaftspraxis, Prof. Dr. P. Langmann and Dr. M. Weikert, Karlstadt, Germany) were recruited for the study. Of the 41 patients, 38 were finally included in our analysis (see method section ‘Assessment of ATI and IFX dynamics’). Only patients with confirmed diagnosis of CD or UC on maintenance therapy with Remicade[®] (Janssen Biologics B.V., Leiden, Netherlands), Remsima[®] (Celltrion, Incheon, South Korea), or Inflectra[®] (Hospira, Lake Forest, IL, USA) were included, whereby disease severity was indicative of IFX application. Patients below legal age, pregnant patients, and patients with less than four TDM/IT measurements were excluded, whereby ATI-positive patients were required to have at least one more TDM/IT recording after the first detection of ATI.

Remission was defined as the absence of clinical and serological signs of inflammation: normal

defecation frequency, absence of visible blood in stool and of intestinal or extraintestinal IBD-associated manifestations, normal levels of C-reactive protein (CRP), and moderate, stable levels of fecal calprotectin (FC). In patients experiencing a relapse in combination with emerging ATI, either IFX dosages were increased or application intervals shortened (normal IFX dosage in maintenance therapy: $5 \text{ mg} \cdot \text{kg}^{-1}$ intravenously every 8 weeks). Reasons for discontinuation of IFX therapy were secondary LOR, serious AR to IFX therapy, or insufficient compliance. In the following, the term ‘LOR’ is used for IFX discontinuation due to secondary LOR. The term ‘total IFX discontinuation’ denotes all cases of IFX discontinuation, due to any of the three aforementioned reasons. Nonresponse to IFX induction (primary LOR) was not considered in this study.

The study was approved by the local Ethics Committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München, approval number 289/19 S). Written informed consent was obtained from all patients. No financial compensation was provided. The reporting of this study conforms to the STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) statement (see checklist in Supplemental Material).¹⁹

Laboratory analyses

IFX and ATI serum concentrations were analyzed at MVZ Medizinisches Labor Oldenburg GmbH (Oldenburg, Germany) with the IDKmonitor® Infiximab drug-level enzyme-linked immunosorbent assay (ELISA) and the drug-tolerant IDKmonitor® Infiximab total ADA ELISA (both from Immundiagnostik AG, Bensheim, Germany), respectively. Furthermore, CRP in serum was measured turbidimetrically with the Tina-quant® C-Reactive Protein assay on a cobas® 8000 device with cobas c 701 analytical modules (all from Roche Diagnostics, Mannheim, Germany). FC was quantified via ELISA with the RIDASCREEN® Calprotectin assay on a DSX® system (R-Biopharm AG, Darmstadt, Germany). CRP and FC were both analyzed at the outpatient clinic at Würzburg where the patients were treated and determined at 89% and 45% of TDM/IT visits of all patients, respectively.

Assessment of ATI and IFX dynamics

IFX and ATI serum levels were monitored proactively, usually before application of the next

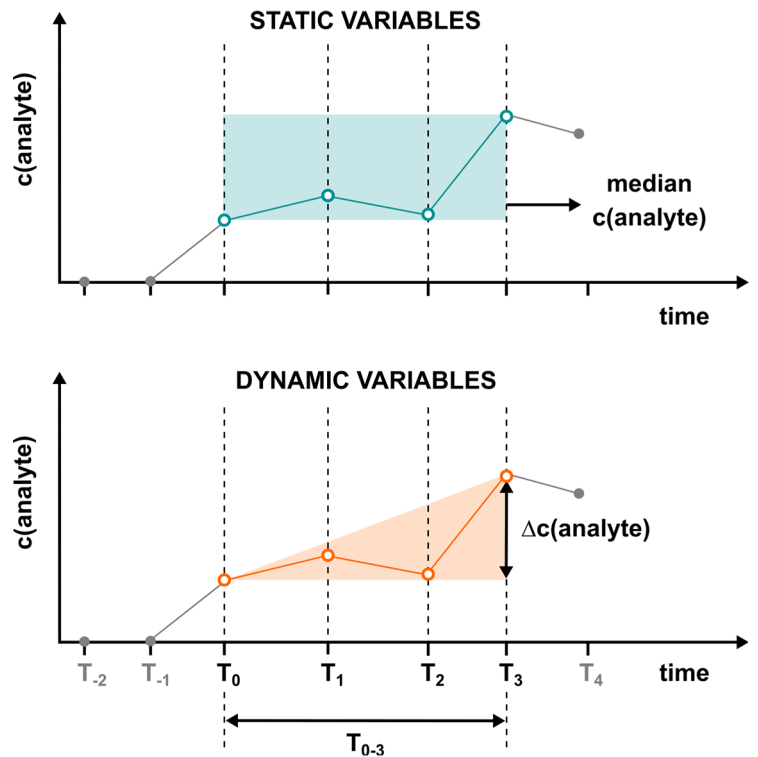


Figure 1. Calculation of static (time-independent) and dynamic (time-dependent) variables. The static variables (ATI_{median} , IFX_{median} , CRP_{median} , FC_{median}) are calculated as median analyte concentration of all available (max. 4) entries for the respective analyte in T_{0-3} . Slopes as dynamic variables (S_{ATI} , S_{IFX}) represent the average analyte (ATI or IFX) concentration change between visits T_0 and T_3 calculated as analyte concentration difference $\Delta c(\text{analyte})$ between T_0 and T_3 divided by the time period T_{0-3} . For clarification, S_{ATI} and S_{IFX} are reported as $\text{AU mL}^{-1} \text{ week}^{-1}$ and $\mu\text{g mL}^{-1} \text{ week}^{-1}$, respectively.

IFX dose. The initial entry in a patient’s TDM/IT protocol corresponds to the first monitoring visit after successful IFX induction. T_0 is defined as therapy duration week at the first detection of ATI. ATI and IFX dynamics were calculated for the time between T_0 and the third consecutive TDM/IT visit after T_0 , here to be denominated as T_{0-3} . Complete T_{0-3} datasets were available for only 38 of the 41 initially included patients. In all ATI-positive patients, as dynamic variables, individual slopes of the two analytes ATI (S_{ATI}) and IFX (S_{IFX}) were calculated as average ATI or IFX level change over T_{0-3} (Figure 1):

$$S_{\text{analyte}} = \frac{\Delta c(\text{analyte})}{T_{0-3}}$$

with analyte = ATI or IFX

In addition, as static variables, (a) median ATI and IFX levels over T_{0-3} (ATI_{median} , IFX_{median}) and

(b) maximal ATI and minimal IFX levels over the entire observation time (ATI_{max} , IFX_{min}) were determined. Furthermore, median CRP and median FC levels were calculated as static variables over T_{0-3} (CRP_{median} , FC_{median}). By definition, T_0 does not exist for patients with nondetectable ATI. As such, their S_{ATI} equals $0 AU mL^{-1} week^{-1}$, and S_{IFX} and IFX_{median} cannot be calculated.

Statistical analysis

Statistical analyses were performed with GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA), R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), and RStudio version 1.3.1093 (RStudio PBC, Boston, MA, USA). To enable comprehensive statistical analyses, measurement results below the assays' limit of quantification (LOQ) were set to $0.3 \mu g \cdot mL^{-1}$ for IFX (LOQ $0.6 \mu g \cdot mL^{-1}$), to $5 AU \cdot mL^{-1}$ for ATI (LOQ $10 AU \cdot mL^{-1}$), to $0.02 mg \cdot dL^{-1}$ for CRP (LOQ $0.04 mg \cdot dL^{-1}$), and to 10 or $20 \mu g \cdot g^{-1}$ for FC (LOQ 20 or $39 \mu g \cdot g^{-1}$, depending on the sample dilution). FC measurements above the measurement range were set to the respective upper limit (800, 840, or $1600 \mu g \cdot g^{-1}$, depending on the sample dilution) for statistical analysis. Nonparametric Kruskal–Wallis (triple-wise) and Mann–Whitney U test (pairwise) were used for comparisons between ATI slope groups for continuous variables. Chi-square and Fisher's exact tests were employed to calculate both triple and pairwise comparisons between ATI slope groups for categorical variables as applicable. Kaplan–Meier curves were compared using the log-rank test. Univariate and multivariate hazard ratios (HRs) were calculated using the Cox-proportional hazards model. The likelihood ratio test was used to test the global statistical significance of univariate analyses. Receiver operating characteristic (ROC) analysis was performed and maximal Youden Index was determined to refine the S_{ATI} cut-off for the prediction of LOR. P values were not corrected for multiple testing and considered significant if <0.05 .

Results

Patient characteristics

Thirty-eight patients were included in the study. The number of TDM/IT visits per patient ranged from 4 to 30 (median, 12), with monitoring intervals ranging from 2.5 to 11.8 weeks (median,

6.0 weeks). In total, 500 TDM/IT results for both ATI and IFX levels were available. For 444 (89%) and 224 (45%) of the 500 TDM/IT visits, CRP serum concentrations and FC concentrations in stool were documented, respectively. A comprehensive summary of the characteristics of the included patients is given in Table 1.

Characteristics of the S_{ATI} groups

Based on the individual values of S_{ATI} , patients were assigned to three groups: ATI-N (nondetectable ATI; $S_{ATI}=0$), ATI- \downarrow (negative S_{ATI}), and ATI- \uparrow (positive S_{ATI}). The characteristics and comparisons of the various S_{ATI} groups are depicted in Table 2.

No significant differences between the three groups were found for age, sex, diagnosis, AR, immunosuppressive comedication (CM), therapy duration, IFX_{min} , S_{IFX} , CRP_{median} , FC_{median} , T_0 , and reactive dosing adjustments. ATI_{median} , ATI_{max} , and S_{ATI} , however, differed significantly between the groups ($p < 0.0001$). The median S_{ATI} in the ATI- \downarrow group was calculated as $-1.031 AU mL^{-1} week^{-1}$ [interquartile range (IQR) = -2.469 to $-0.0421 AU mL^{-1} week^{-1}$] and in the ATI- \uparrow group as $4.335 AU mL^{-1} week^{-1}$ (IQR = 0.631 – $8.617 AU mL^{-1} week^{-1}$). Furthermore, the rates of LOR and IFX discontinuation in total were significantly different between the groups ($p=0.004$ and $p=0.01$, respectively). For total IFX discontinuation, differences between the ATI slope groups can be attributed to a significantly lower number of patients discontinuing the therapy in the ATI- \downarrow group compared with the ATI- \uparrow group (8.3% versus 70.0%, respectively; $p=0.0062$). With LOR, however, both the ATI- \uparrow group and the ATI-N group exhibited a significantly higher portion of therapy discontinuation (60% with $p=0.028$ and 18.8% with $p=0.046$, respectively) compared with the ATI- \downarrow group (0%). The median time after T_3 until LOR was 22.3 weeks (IQR = 15.0–63.5 weeks). LOR types according to Ma and colleagues²⁰ for all patients are provided in the Supplemental Material (Table S1). We observed non-immune-mediated pharmacokinetic failure in all ATI-N LOR patients. LOR in ATI- \uparrow patients could be attributed to immune-mediated pharmacokinetic failure in 66.7% of cases, whereas 33.3% experienced mechanistic failure. IFX_{median} was significantly higher in the ATI- \downarrow group ($5.4 \mu g \cdot mL^{-1}$) than in the ATI- \uparrow group ($2.1 \mu g \cdot mL^{-1}$, $p=0.0076$).

Exemplary individual ATI and IFX courses of patients in the ATI-N, ATI-↓, and ATI-↑ groups are depicted in the Supplemental Material (Figure S2) to illustrate the calculation of S_{ATI} .

Total IFX discontinuation-free and LOR-free survival

Survival of the three ATI groups was assessed by Kaplan–Meier analysis for LOR-free and IFX discontinuation-free survival. Significant differences were only observed for LOR ($p=0.021$, Figure 2(a)), but not for total IFX discontinuation ($p=0.088$; Figure 2(b)). Pairwise comparisons of LOR-free survival yielded a significantly lower risk of LOR in the ATI-↓ group compared with the ATI-↑ group ($p=0.015$). LOR-free survival of ATI-N and ATI-↑ and of ATI-N and ATI↓, however, did not differ significantly ($p=0.098$ and $p=0.12$, respectively).

Cox regression

To further investigate the association of S_{ATI} and IFX discontinuation, univariate and bivariate HRs were calculated (Table 3). In a univariate analysis with respect to outcome LOR, not only the ATI-related parameters ATI_{median} ($p=0.02$), ATI_{max} ($p=0.001$), and S_{ATI} ($p=0.002$), but also age ($p=0.03$), diagnosis CD ($p=0.01$), and CRP_{median} ($p=0.02$) were found to be significantly associated with LOR. Parameters significantly associated with LOR in univariate analysis were included in subsequent bivariate analyses (Table 4). The association of S_{ATI} and LOR, however, remained significant even after correcting for age, diagnosis CD, CRP_{median} , and ATI_{median} ($p=0.01$, $p=0.01$, $p=0.02$, and $p=0.03$, respectively). S_{ATI} was not correlated significantly with LOR anymore, when its HR was corrected for ATI_{max} ($p=0.09$). For outcome IFX discontinuation due to any reason, the only significant associations were found with S_{ATI} (Table 3; $p=0.03$). To further investigate the correlation of LOR with diagnosis in univariate analysis, nonparametric Kruskal–Wallis test was additionally performed to compare S_{ATI} , ATI_{median} , and ATI_{max} between CD and UC patients. However, no statistically significant difference was observed (see Table S3 in Supplemental Material).

Optimal time interval for S_{ATI} calculation

Besides T_{0-3} , S_{ATI} was additionally calculated for the time periods T_{0-1} and T_{0-2} (Figure 3) to

Table 1. Patient characteristics.

Characteristics	Summary statistics
Total, n (%)	38 (100.0)
Age, years, median (IQR)	39 (28–57)
Female sex, n (%)	20 (52.6)
Diagnosis CD, n (%)	28 (73.7)
IFX discontinuation, n (%)	14 (36.8)
Due to LOR ^a	9 (23.7)
Due to AR ^a	5 (13.2)
Due to poor compliance	1 (2.6)
AR to IFX, ^b n (%)	11 (28.9)
Immunosuppressive comedication, n (%)	21 (55.3)
Therapy duration, weeks, median (IQR)	68.2 (32.2–108.8)

AR, adverse reactions; CD, Crohn's disease; IFX, infliximab; IQR, interquartile range; LOR, loss of response.
^aOne patient discontinued therapy due to both LOR and AR and was counted for both end points.
^bIncludes cutaneous reactions, anaphylactic reactions, and joint pain.

investigate the minimum monitoring time period for robust LOR prediction. Univariate Cox-proportional hazards models were then calculated for the end point LOR using the various S_{ATI} calculation bases. Only S_{ATI} calculated over T_{0-3} yielded a significant association with LOR ($p=0.002$; Table 5). S_{ATI} values calculated for the different time periods are shown in the Supplemental Material (Tables S4 and S5).

Refinement of S_{ATI} cut-off

The cut-off of S_{ATI} for LOR was further optimized via ROC analysis (Figure 4). Including ATI-positive cases only ($n=22$), S_{ATI} identifies patients experiencing LOR with an area under the curve (AUC) of 0.948 ($p=0.002$). The optimal S_{ATI} cut-off was calculated as $2.008 \text{ AU mL}^{-1} \text{ week}^{-1}$, yielding a sensitivity of 83.3% and a specificity of 93.8%.

Discussion

We investigated whether ATI dynamics, quantified via a proactive TDM combined with IT, are able to predict LOR in patients with IBD under IFX medication and how their predictive

Table 2. Patient characteristics by ATI slope (S_{ATI}) group.

Characteristics	Summary statistics			p values			
	ATI-N	ATI-↓	ATI-↑	All	N versus ↓	N versus ↑	↓ versus ↑
Total, n (%)	16 (42.1)	12 (31.6)	10 (26.3)				
Age, years, median (IQR)	39 (30 to 57)	33 (27 to 50)	43 (26 to 63)	0.7			
Female sex, n (%)	8 (50.0)	7 (58.3)	5 (58.3)	0.9			
Diagnosis CD, n (%)	13 (81.3)	10 (83.3)	5 (50.0)	0.1			
AR to IFX, n (%)	3 (18.8)	6 (50.0)	2 (20.0)	0.2			
CM, n (%)	12 (75.0)	6 (50.0)	3 (30.0)	0.07			
Therapy duration, weeks, median (IQR)	63.8 (28.6 to 105.8)	75.6 (38.9 to 93.9)	66.0 (31.8 to 117.1)	0.9			
IFX _{median} , µg·mL ⁻¹ , median (IQR)	NA	5.4 (3.9 to 9.7)	2.1 (1.0 to 4.0)	NA	NA	NA	0.0076**
IFX _{min} , µg·mL ⁻¹ , median (IQR)	1.3 (0.4 to 2.1)	1.1 (0.3 to 3.2)	0.6 (0.3 to 1.5)	0.4			
S_{IFX} , µg mL ⁻¹ week ⁻¹ , median (IQR)	NA	-0.247 (-0.595 to -0.011)	-0.021 (-0.147 to 0.115)	NA	NA	NA	0.1440
ATI _{median} , AU·mL ⁻¹ , median (IQR)	5.0 (5.0 to 5.0)	5.0 (5.0 to 9.1)	42.5 (20.3 to 140.6)	<0.0001***	0.0081**	<0.0001***	0.0017**
ATI _{max} , AU·mL ⁻¹ , median (IQR)	5.0 (5.0 to 5.0)	45.6 (17.7 to 57.7)	205.7 (58.4 to 506.9)	<0.0001***	<0.0001***	<0.0001***	0.0090**
S_{ATI} , AU mL ⁻¹ week ⁻¹ , median (IQR)	0.000 (0 to 0)	-1.031 (-2.469 to -0.421)	4.335 (0.631 to 8.617)	<0.0001***	<0.0001***	<0.0001***	<0.0001***
CRP _{median} , mg·dL ⁻¹ , median (IQR)	0.29 (0.05 to 0.74)	0.21 (0.06 to 0.31)	0.35 (0.16 to 1.13)	0.3			
FC _{median} , µg·g ⁻¹ , median (IQR)	288 (51 to 733)	156 (88 to 493)	246 (78 to 489)	0.9			
T_0 , weeks, median (IQR)	NA	1.1 (0.0 to 13.8)	8.9 (0.0 to 21.4)	NA	NA	NA	0.4799
DI shortening ^a	14 (87.5)	11 (91.7)	9 (90.0)	0.9			
Frequency ^a	1.0 (0.0 to 1.0)	1.5 (1.0 to 2.8)	2.0 (1.0 to 3.0)	0.6			
Dose increase ^a	6 (37.5)	6 (50.0)	4 (40.0)	0.8			
Frequency ^a	0.0 (0.0 to 1.0)	0.5 (0.0 to 1.0)	0.0 (0.0 to 2.0)	0.9			
IFX discontinuation, n (%)	6 (37.5)	1 (8.3)	7 (70.0)	0.01*	0.18	0.23	0.0062**
Due to LOR	3 (18.8)	0 (0.0)	6 (60.0)	0.004**	0.24	0.046*	0.0028**
Due to AR	2 (12.5)	1 (8.3)	2 (20.0)	0.7			
Due to poor compliance	1 (6.3)	0 (0.0)	0 (0.0)	0.5			

AR, adverse reactions; ATI, antibodies to infliximab; ATI-N, ATI nondetectable; CD, Crohn's disease; CM, immunosuppressive comedication; DI, dosing interval; IFX, infliximab; IQR, interquartile range; LOR, loss of response; S_{ATI} , slopes of ATI; S_{IFX} , slopes of IFX.
^aVariables DI shortening and dose increase indicate the number of patients who underwent intervention, while respective frequencies indicate the number of interventions per patient. Significance levels are indicated by * for 0.01 < p < 0.05, ** for 0.001 < p ≤ 0.01, and *** for p ≤ 0.001.

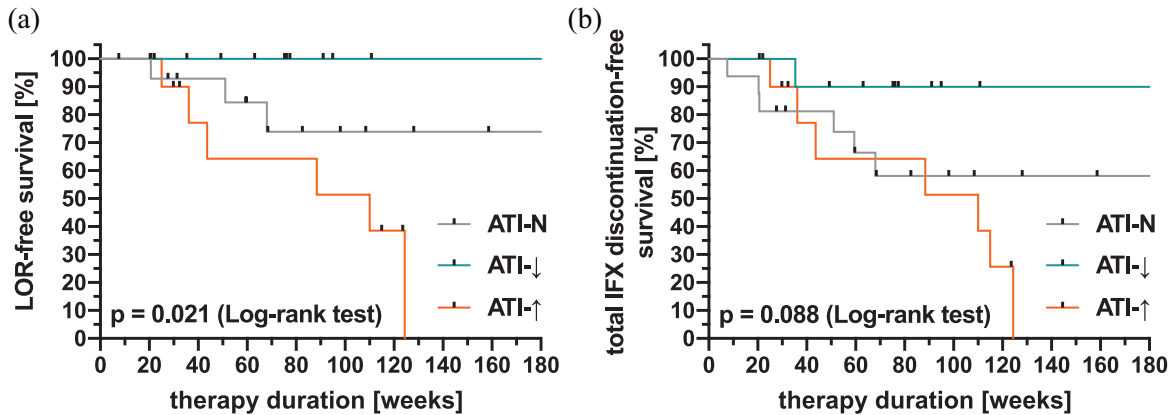


Figure 2. Kaplan–Meier curves for end points LOR (a) and total IFX discontinuation (b). Number of reported events per analysis were 9 for LOR and 14 for IFX discontinuation. Right censored data points are indicated by black ticks.

performance compares with other measures of therapy success. S_{ATI} was defined as a novel parameter, representing ATI dynamics during approximately 17 weeks after the first ATI-positive TDM/IT result and was found to be strongly associated with LOR. Increasing ATI concentrations in serum indicated a higher risk of LOR. Notably, S_{ATI} was the best predictor for LOR among all considered ATI, IFX, and inflammation parameters.

The predictive potential of S_{ATI} for LOR is supported by univariate and multivariate comparisons and ROC analysis. Among ATI-positive patients, an S_{ATI} cut-off of approximately $2.0 \text{ AU mL}^{-1} \text{ week}^{-1}$ yielded high sensitivity and specificity for LOR. In addition to confirming the predictive potential of S_{ATI} , univariate and multivariate analyses revealed that S_{ATI} exhibits the best predictive performance among all evaluated laboratory parameters. Included laboratory parameters were usually calculated for T_{0-3} , that is, the same period of time as S_{ATI} . Only ATI_{\max} and IFX_{\min} refer to the entire observation period of the respective patient. A significant association with the risk of LOR was detected for both S_{ATI} and ATI_{\max} . The magnitude of the HR for S_{ATI} is as well comparable to that of ATI_{\max} (1.209 and 1.004, respectively). However, it is generally unclear when ATI_{\max} is or will be reached, not to mention if it is reached within T_{0-3} . As such, S_{ATI} constitutes the more feasible parameter for the clinician. Overall, our results suggest that the value of ATI dynamics in current TDM/IT protocols for IBD patients is greatly underestimated.

Our study proposes S_{ATI} as a simple, new laboratory index to predict LOR.

The European Crohn's and Colitis Organisation (ECCO) and American Gastroenterological Association (AGA) do not recommend proactive TDM/IT due to the lack of sufficient data.^{21,22} However, a positive association of ATI titers and secondary LOR with IFX and, consequently, the benefit of proactive IT in IBD have been described in several studies.^{15–17,23,24} The detailed dynamics of ATI courses in single patients, though, are still not fully understood, even for IFX as widely prescribed biologic. Nevertheless, evidence suggests that proactive IT provides the best assessment of anti-drug antibody dynamics, rather than sporadic, reactive ‘snap-shot’ measurements.²⁵ For IFX and adalimumab, proactive TDM/IT was found to be beneficial with respect to prevention of secondary LOR, less frequent ATI emergence, and better mucosal healing.^{26–28} In our study, the proactive TDM/IT regimen enabled precise and early detection of T_0 , which occurred at a median of 3.4 weeks after the first TDM/IT visit during maintenance therapy, that is, approximately 16 weeks after the first IFX infusion. This result is in good agreement with other studies with similarly frequent proactive monitoring policy.^{18,29} A time point or interval for therapeutic decision-making was not precisely defined in the aforementioned studies. Our results, on the contrary, enable prediction of LOR approximately 17 weeks after T_0 . The studies focusing on ATI dynamics are limited in number and primarily investigate the transient *versus* persistent nature of ATI. In

Table 3. Univariate analysis of IFX discontinuation.

LOR	LOR				Total IFX discontinuation			
	HR	95% CI	<i>p</i>	C	HR	95% CI	<i>p</i>	C
Age	1.046	1.002–1.093	0.03*	0.774	1.009	0.976–1.042	0.6	0.558
Female sex	0.794	0.204–3.087	0.7	0.543	0.964	0.328–2.832	0.9	0.492
Diagnosis CD	0.165	0.039–0.695	0.01*	0.736	0.339	0.113–1.016	0.06	0.599
AR	0.280	0.035–2.250	0.2	0.587	1.201	0.400–3.613	0.7	0.534
CM	1.309	0.347–4.944	0.7	0.552	1.352	0.465–3.933	0.6	0.558
CRP _{median}	4.529	1.391–14.75	0.02*	0.772	2.458	0.937–6.448	0.09	0.588
FC _{median}	1.001	0.999–1.002	0.3	0.747	1.001	0.999–1.002	0.5	0.598
T_0	0.995	0.961–1.031	0.8	0.629	0.987	0.952–1.024	0.4	0.685
DI shortening	3×10^7	0–inf.	0.4	0.530	0.649	0.079–5.324	0.7	0.510
Frequency	0.841	0.493–1.435	0.5	0.571	0.797	0.512–1.242	0.3	0.611
Dose increase	0.369	0.088–1.551	0.2	0.682	0.321	0.097–1.058	0.05	0.702
Frequency	0.795	0.327–1.936	0.6	0.639	0.702	0.336–1.466	0.3	0.673
ATI _{median}	1.008	1.002–1.013	0.02*	0.647	1.005	1.000–1.010	0.1	0.519
ATI _{max}	1.004	1.002–1.007	0.001**	0.630	1.003	1.001–1.005	0.1	0.519
S_{ATI}	1.209	1.082–1.351	0.002**	0.783	1.122	1.029–1.224	0.03*	0.644
IFX _{median}	0.717	0.461–1.115	0.08	0.766	0.853	0.628–1.158	0.3	0.660
IFX _{min}	0.630	0.288–1.378	0.2	0.693	0.994	0.635–1.556	1.0	0.518
S_{IFX}	6.708	0.450–100	0.1	0.573	0.591	0.092–3.780	0.6	0.562

AR, adverse reactions; C, model concordance; CD, Crohn's disease; CI, confidence interval; CM, immunosuppressive comedication; DI, dosing interval; HR, hazard ratio; IFX, infliximab; LOR, loss of response; S_{ATI} , slopes of ATI; S_{IFX} , slopes of IFX. Significance levels are indicated by * for $0.01 < p \leq 0.05$ and ** for $p \leq 0.01$.

observational and prospective studies, transient ATI seem to be less frequently associated with LOR and to exhibit lower titers compared with persistent ATI.^{16,18,29} Although not the subject of this work, we observed that in the ATI-↓ group 83.3% of the patients had ATI-negative sera at the end of follow-up, compared with only 10% in the ATI-↑ group (data not shown). The respective, dominant LOR type observed in each S_{ATI} group (immune-mediated pharmacokinetic failure in ATI-↑ and non-immune-mediated pharmacokinetic failure in ATI-N patients; see Table S1 in Supplemental Material) supports these results. Also, the significantly lower median ATI

titers in the ATI-↓ and the significantly higher LOR rates in the ATI-↑ group are in good agreement with the reports cited above. Beyond that, our data suggest that S_{ATI} may constitute an early predictor of ATI persistence. Our study suggests that proactive IT can contribute to an improved pharmacologic management and might influence clinical decision-making. It remains to be elucidated whether proactive IT can also influence clinical targets such as the rate of mucosal healing or histologic remission in patients with IBD. If this could be shown in further studies, the current recommendations of ECCO and AGA against proactive IT would be obsolete.

Table 4. Bivariate analysis of LOR risk.

x	HR	95% CI	$p(S_{ATI})$	$p(x)$	C
–	1.209	1.082–1.351	0.002**	–	0.783
Age	1.172	1.034–1.330	0.01*	0.4	0.840
Diagnosis CD	1.168	1.036–1.317	0.01*	0.08	0.851
CRP _{median}	1.165	1.024–1.325	0.02*	0.3	0.845
ATI _{median}	1.174	1.018–1.355	0.03*	0.5	0.777
ATI _{max}	1.136	0.982–1.313	0.09	0.07	0.755

C, model concordance; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio.

HRs for LOR are presented, adjusted for the enlisted covariates (x). Data for total IFX discontinuation are not shown, since S_{ATI} was the only significant variable in univariate analysis. Significance levels are indicated by * for $0.01 < p < 0.05$ and ** for $p \leq 0.01$.

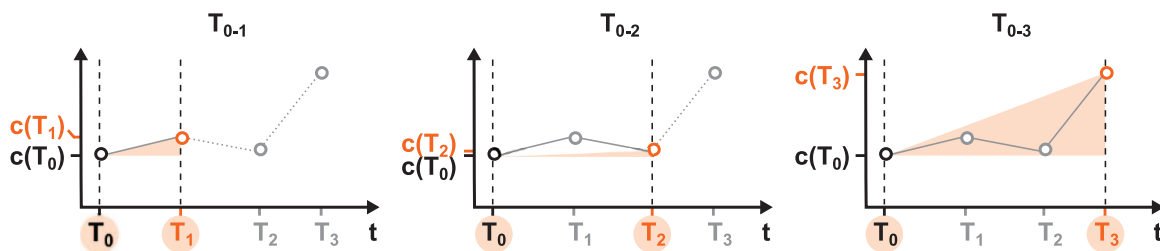


Figure 3. Principle of data selection in the three different S_{ATI} calculation bases T_{0-1} (left panel), T_{0-2} (center panel), and T_{0-3} (right panel). Each panel contains the same hypothetical ATI level course in an individual patient and depicts the magnitude of the corresponding average slope (shaded triangle). The two TDM/IT visits considered for the respective S_{ATI} calculations (T_0 and end point) are highlighted on the time (t) axis.

Table 5. Characteristics for the three groups according to S_{ATI} calculation base.

Characteristics	Summary statistics		
	T_{0-1}	T_{0-2}	T_{0-3}
Patients, n (%)	41 (100.0)	39 (100.0)	38 (100.0)
LOR, n (%)	11 (26.8)	10 (25.6)	9 (23.7)
Length T_{0-x} , weeks, median (IQR)	5.3 (4.1–8.6)	12.0 (8.9–16.0)	17.2 (12.9–22.6)
HR [95% CI]	1.018 [0.999–1.037]	1.078 [0.918–1.267]	1.209 [1.082–1.51]
p value	0.1	0.4	0.002**
C	0.621	0.548	0.783

C, model concordance; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; LOR, loss of response. x denotes the x th visit after T_0 . Significance level is indicated by ** for $p \leq 0.01$.

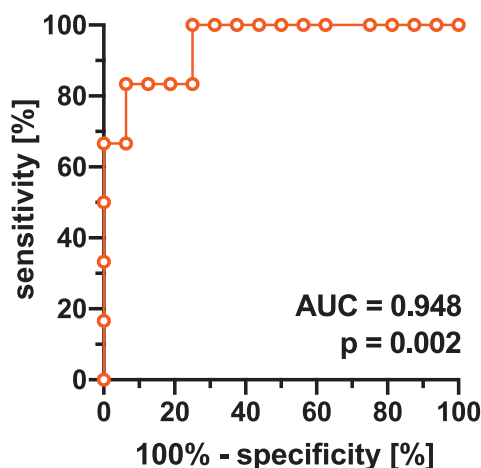


Figure 4. ROC curve for ATI-positive patients ($n=22$).

Besides ATI, several other predictors of LOR have been described, with IFX trough level being the most important one.^{24,30} Considering the lack of standardized strategies for ATI management, IFX therapies are sometimes merely IFX trough level guided.^{1,10-14} Notably, IFX levels and related indices did not predict LOR in our study. Regarding the S_{ATI} group comparisons, this surprising observation may, on the one side, be caused by limiting the analyzed data to the time window T_{0-3} . On the other side, this result may be due to the fact that IFX_{median} and S_{IFX} could not be calculated for ATI-N patients; hence, these patients were not included in the comparisons. However, univariate Cox regression did not yield significant correlations of IFX-dependent parameters with LOR, either, and no patients were excluded for these calculations. Possibly, the aggressive, proactive dose intensification regime imposed variance on IFX trough levels in this work. Even in absence of ATI, IFX courses can fluctuate (see patient P-12 in Figure S2 in Supplemental Material). The importance of ATI monitoring suggested by our study is supported, for example, by Magro and colleagues,³¹ who found ATI and FC monitoring to be more relevant for therapeutic escalation than IFX trough levels. Apart from IFX trough levels, both FC and CRP are known to be associated with therapeutic outcome.^{3,14,16} In our cohort, however, only CRP_{median} , but not FC_{median} was correlated with LOR. This may be attributed to the smaller number of available FC results in our cohort. In our univariate analysis, furthermore, age and diagnosis were associated with LOR. Higher age

(>60 years) has been described before as risk factor for anti-TNF therapy discontinuation due to AR or LOR, thereby confirming our findings.^{32,33} The increased LOR risk for UC over CD patients that was surprisingly found in univariate analysis is not supported by further literature. Grinman and colleagues,³⁴ however, described higher ATI and FC levels for UC than for CD patients, yet without differences in therapy success. The aforementioned and our study both analyzed a small portion of UC patients (Grinman and colleagues: $n=10$, accounting for 10.5% of included patients; this study: $n=10$, 26.3%). Hence, the higher ATI titer for UC patients in the study by Grinman and colleagues and the univariate correlation with LOR for diagnosis UC in our study may be the incidental result of underpowered statistics regarding the variable diagnosis. In contrast, Vande Castele and colleagues¹⁸ reported results consistent with ours. There were no differences in ATI and IFX levels between CD and UC in their larger cohort (see Table S3 in Supplemental material). Notably, S_{ATI} outperformed other variables in our bivariate analysis. Moreover, S_{ATI} predicted LOR despite therapeutic interventions.

A possible explanation for the observed association is that the dynamics of the initial immune response against IFX are characteristic for its severity and responsiveness to treatment intervention, such as dose adjustments. First, a steep rise of ATI, reflected by a positive S_{ATI} , may be indicative of more aggressive immunogenicity by rapidly enhancing IFX clearance.³⁵ Second, the 17-week timeframe of T_{0-3} comprises first interventions to counteract emerging ATI for some patients. Rising ATI despite dose adjustments in the beginning of maintenance therapy may be indicative of lacking ATI responsiveness to dose adjustments and of ATI persistence, which both are associated with higher LOR rates. We therefore suggest S_{ATI} as a valuable parameter for clinical decision-making, in combination with accurate clinical evaluation. In case of $S_{ATI} > 2.0 \text{ AU mL}^{-1} \text{ week}^{-1}$, IFX therapy may be maintained if the patient remains in remission.¹² If S_{ATI} above the critical cut-off is accompanied by worsening symptoms, therapeutic intervention may be considered, for example, adjustment of IFX dose or immunosuppressive comedication, or switch to a different biologic. In summary, a high S_{ATI} should alert the gastroenterologist to pay close attention to the patient.

Strengths of this study encompass its real-world nature and the consistently proactive, high-frequency TDM/IT. Some other relatively monitoring-intensive studies^{16,18,36} determined ATI serum levels between 1 and 5 times per patient (median of 5 available ATI titers per patient in Roblin and colleagues),¹⁶ with average TDM/IT intervals of at least 3 months reported for Roblin and colleagues¹⁶ and Pugliese and colleagues.³⁶ Vande Castele and colleagues¹⁸ published a more monitoring-intensive retrospective study, in which an average of 14 TDM/IT samples per patient were analyzed over a study duration of 12 years. In this study, a remarkably high number (median, 12) and frequency of visits (median, 6.0 weeks) per patient were analyzed. Of note, we obtained highly significant findings despite our small cohort size. Overall, our pilot analysis builds an intriguing base for further studies of S_{ATI} with larger patient cohorts.

Some limitations of our study, however, have to be mentioned. First, the small cohort size may conceal further significant correlations and did not allow to include more than two variables at a time in the multivariate analysis. The presented bivariate analysis therefore has to be interpreted with caution. Second, the retrospective and monocentric design of this study may have introduced some bias. Third, monitoring intervals longer than T_{0-3} for calculation of S_{ATI} were not assessed due to the lack of sufficient data. Fourth, our collective included both CD and UC patients. This approach has also been chosen in other studies, but may introduce some bias.^{18,23,34} Finally, all reported ATI-related values are only valid for the specific ELISA employed. Since the majority of IFX IT, like in our study, only targets ATI quantification, but not characterization, the question arises whether more information about ATI would improve patient care. ATI comprise patient-individual polyclonal antibody populations that can exhibit different avidities and epitope coverage. Assessment of these characteristics requires alternative methodology, for example, surface plasmon resonance-based biosensors.³⁷⁻³⁹ In addition, an adequate consensus methodology is required to establish the overdue gold standard for TDM/IT in IFX therapy. First attempts have already been made.⁴⁰

Beyond IFX therapy, it will be exciting to track further efforts on the deciphering of patient-individual anti-drug antibody dynamics and characteristics for

any biologic. Learning more about their similarities or differences and their role in therapy failure will build the basis for a sustainable improvement in biologic therapy.^{37,41}

Conclusion

To conclude, this study suggests S_{ATI} as new diagnostic index for ATI dynamics, allowing to predict LOR in IBD patients. S_{ATI} was calculated from two TDM/IT visits over a short period of time (17 weeks) and provides, along with clinical symptoms, a decision-making aid for further therapeutic management. Thus, S_{ATI} enables quick and standardized reaction to the first detection of ATI. To ensure early ATI detection, we recommend proactive ATI monitoring at every IFX infusion visit. S_{ATI} will then provide reliable predictive information.

Acknowledgements

Simon Wiegrebe and Kurt Ulm (both in Munich) provided highly appreciated statistical consulting. The authors also owe thanks to Susanne Weber (Munich) and Gunnar Brandhorst (Oldenburg) for fruitful discussions, as well as to all medical staff in Würzburg involved in patient care. We are deeply indebted to our patients for enabling the present study. Melina K. Grasmeier and Anna F. Langmann contributed equally to this work.

Author contributions

MKG, AFL, MAT, PL, and PBL contributed to the study design. PL and AFL educated patients, collected consent forms, and applied for study approval by the ethics committee. PL was responsible for patient recruitment. AFL and PL collected data. MKG analyzed the data. MKG, MAT, MT, and PBL drafted the manuscript. All authors were involved in data interpretation, contributed important intellectual content to the manuscript through critical revision, and approved the final article.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

The corresponding author provides datasets for this study at request.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the Stiftung für Pathobiochemie und Molekulare Diagnostik (SPMD, Bonn) within the project ADAmom (Monitoring TNF inhibitor serum concentrations and characterization of anti-drug antibodies with surface plasmon resonance for patient-tailored therapy of inflammatory autoimmune diseases).

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Supplemental material


Supplemental material for this article is available online.

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