

Rapid point-of-care anti-infliximab antibodies detection in clinical practice: comparison with ELISA and potential for improving therapeutic drug monitoring in IBD patients

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Abstract: Anti-drug antibodies can interfere with the activity of anti-tumor necrosis factor (TNF) agents by increasing drug clearance *via* direct neutralization. The presence of anti-drug antibodies is clinically relevant when trough drug concentrations are undetectable or sub-therapeutic. However, traditional immunoassay is not easily and rapidly accessible, making the translation of the results into treatment adjustment difficult. The availability of a point-of-care (POC) test for therapeutic drug monitoring (TDM) might represent an important step forward for improving the management of inflammatory bowel disease (IBD) patients in clinical practice. In this pilot study, we compared the results obtained with POC tests with those obtained by enzyme-linked immunosorbent assay (ELISA) in a group of IBD patients treated with Infliximab (IFX). We showed that POC test can reliably detect presence of antibody-to-IFX with 100% of specificity and 76% sensitivity, in strong agreement with the ELISA test (k -coefficient = 0.84).

Keywords: IBD, anti-TNF, anti-drug antibodies, through levels, therapeutic drug monitoring, point-of-care

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Introduction

The introduction of anti-tumor necrosis factor (TNF) alpha agents has significantly changed the outcome of inflammatory bowel disease (IBD) patients, leading to an increased rate of remission and improved quality of life.^{1,2} However, previous studies described 10–30% of patients who fail to respond initially and an annual rate of 10–20% of the initial responders tends to stop treatment due to loss of response.³

Thus, a closer monitoring of patient's anti-TNF trough levels (TL) and, in patients treated with Infliximab (IFX), antibody-to-Infliximab (ATI) has been suggested and has been found cost-effective in patient management.^{4,5} Low IFX TL and high ATI are associated with future loss of

response to treatment, whereas high TL and low ATI are correlated with future response to treatment during intensification therapy.^{6–9} The trough concentrations of these drugs may vary due to different factors, including drug clearance through immune and non-immune-mediated mechanisms.¹

Several methods for therapeutic drug monitoring (TDM), measurement of drug trough concentration, and the presence of antibodies against a specific drug, have been developed, validated, and made commercially available. Enzyme-linked immunosorbent assay (ELISA) techniques represent the most commonly used.¹⁰ However, ELISA tests are time-consuming, require the collection of a determinate number of blood

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samples before a batch can be processed and do not provide real-time results. In this context, the availability of a point-of-care (POC) test for TDM might represent an important step forward for improving the management of IBD patients in clinical practice since they can be performed during a routine outpatient visit and make the result immediately available and useful for the decision-making process.¹¹ Moreover, POC could be particularly valuable in the acute setting. For instance, patients with acute severe colitis may exhibit rapid clearance of anti-TNF alpha, and POC quantification of IFX serum concentration could advise the decision of dose escalation by accelerated infusion.¹⁰

The aim of the present pilot cross-sectional study was to compare the results obtained with POC tests with those available with ELISA assays.

Methods

Consecutive unique IBD patients referring to our infusion center were enrolled prospectively. Inclusion criteria were age ≥ 18 years and confirmed diagnosis of ulcerative colitis (UC) or Crohn's disease (CD) based on clinical, endoscopic, and histological examinations,¹² and treatment with IFX for at least 4 months for a moderate–severe disease activity. Exclusion criteria were pregnancy and refusal to sign the informed consent form. The study protocol was performed accordingly to the ethical guidelines of the 1964 Declaration of Helsinki (6th revision, 2008) and approved by the local Ethics Committee (protocol number 3312/AO/14).

Demographics, activity score (Harvey Bradshaw Index for CD patients, partial Mayo score for UC patients), laboratory data [C-reactive protein (CRP) and fecal calprotectin levels], and therapies were collected.

Whole blood and serum samples were collected immediately before IFX infusion; 30 μ l of whole blood was immediately used to perform the POC test following the manufacturer's instructions (Promonitor Quick Anti-IFX, Grifols Diagnostic, Milan, Italy). Serum aliquots were stored at -20°C for solid-phase-ELISA analysis (Promonitor IFX and Anti-IFX, Grifols Diagnostic). The Promonitor Quick Anti-IFX is a POC test for the qualitative detection of anti-IFX antibodies based on lateral flow (LF) technology with limit of detection (LoD)

of 23 arbitrary units (AU)/ml [95% confidence interval (CI): 20.6–26.9]; the results are read visually at 30 min after adding 30 μ l of whole blood or 15 μ l serum. This POC assay has been shown previously to be suitable for the detection of ATI either for originator drug or biosimilars.¹³

The Promonitor Anti-IFX is an ELISA for the quantitative determination of anti-IFX antibodies in serum samples with LoD of 5 AU/ml. Quantitative results were categorized as positive (ATI > 10 AU/ml) or negative (ATI ≤ 10 AU/ml). The Promonitor IFX is an ELISA for the quantitative detection of IFX trough levels (range of detection from 0.035 μ g/ml to 14.4 μ g/ml); results were categorized as therapeutic (IFX levels 3–7 μ g/ml), sub-therapeutic (IFX levels < 3 μ g/ml), and supra-therapeutic (IFX levels > 7 μ g/ml).¹⁴

The STATA 11 software package was used for statistical analysis (StataCorp LLC, College Station, TX, USA). Categorical and continuous variables were expressed as proportion with percentage and mean with standard deviation (SD), respectively. We used Chi-Square test to compare categorical data. The level of concordance between POC and ELISA test was obtained using the *k* coefficient. Finally, we analyzed POC sensitivity (SE) and specificity (SP), implemented with the degree of agreement with positive (PPV) and negative (NPV) predicted value,¹⁵ considering the ELISA test as the gold standard.

Results

A total of 100 IBD patients (50 CD, 50 UC) attending our infusion center to receive scheduled IFX from June 2019 to November 2019 were enrolled. Demographics and clinical data are reported in Table 1. We found a significant agreement between ELISA-ATI and POC-ATI (*k* coefficient = 0.84, $p < 0.001$), with POC-ATI specificity and sensitivity of 100% and 76%, respectively.

Overall, 17 (17%) samples tested positive for ATI with the reference ELISA method and 43 (43%) showed sub-therapeutic drug levels (TL < 3 μ g/ml). The 83 patients categorized as negative by ELISA (ATI levels ≤ 10 μ g/ml) had therapeutic or supra-therapeutic drug levels. All ATI negative samples as assessed by ELISA were confirmed by the POC assay, with 95.4% NPV (Table 2). ATI levels > 10 μ g/ml were found in 17 patients by

immunoassay, whereas 13 patients tested positive by POC (Table 2) and all had sub-therapeutic TL. One out of the four discrepancies was due to ATI concentration (13.66 AU/ml) below the LoD of the POC test. No significant differences were found in terms of demographics, type or extent of disease, duration of IFX therapy, concomitant use of immunomodulators, or baseline CRP and calprotectin values between patients with TL < 3 µg/ml in presence or absence of ATI.

In order to assess the discrepancies, we tested stored serum samples collected at the previous infusion and at the time of the study index infusion. Among the three patients with high-titer detectable ATI (61.51 AU/ml, 383.6 AU/ml, and 470.8 AU/ml) by immunoassay, we found two out of three patients become positive for ATI by the POC assay, consistent with ELISA results (Table 3), with only one patient (ATI level 470.8 AU/ml) remaining negative even when the serum was tested, thus representing a genuine failure of the POC test.

Discussion

In this pilot study, we report the comparison between a rapid monitoring technique and a commonly used ELISA for the measurement of ATI in IBD patients. The results obtained by POC assay showed strong agreement (k coefficient = 0.84) with those obtained by ELISA assay, with 100% specificity and 76% sensitivity. Two out of the four discrepancies found were due to the type of biological samples tested, with POC correctly detecting ATI when serum sample was used instead of whole blood, and one patient resulted in a false negative result due to the ATI concentration below the LoD of the POC assay.

A limited number of biologics are approved for the treatment of IBD and current data demonstrate clearly that patients who fail anti-TNF do not respond as well to subsequent therapies.¹⁶ Thus, TDM has received increasing attention as a strategy to optimize biologic agents and maximize their effectiveness. Indeed, inadequate drug exposure and sub-therapeutic drug concentrations may represent the reason for loss of response (LOR), with the formation of antibodies against the drug representing the most common mechanism of low or undetectable drug concentration. Several studies have shown that higher biologic drug concentrations are associated with favorable

Table 1. Demographic and clinical characteristics of the study population.

Number of patients	100
Type of disease	
CD, <i>n</i>	50
UC, <i>n</i>	50
Median age (25th–75th percentiles)	44 (31–57)
Sex (male/female), <i>n</i>	69/31
Disease duration (months), <i>n</i> (range)	108 (47–201)
Duration of anti-TNF therapy (months), <i>n</i> (range)	18 (7–49.5)
Type anti-TNF, <i>n</i> (%)	
Remsima	32 (32)
Flixabi	59 (59)
Remicade	9 (9)
Disease activity according to pMayo in UC, <i>n</i> (%)	
Remission	13 (26)
Mild	22 (44)
Moderate	12 (24)
Severe	3 (6)
Disease activity according to HBI in CD, <i>n</i> (%)	
Remission	41 (82)
Mild	7 (14)
Moderate	2 (4)
Severe	–
Median fecal calprotectin, <i>n</i> (range)	109 (47–471.5)
UC localization, <i>n</i> (%)	
E1	11 (22)
E2	17 (34)
E3	22 (44)
CD behavior, <i>n</i> (%)	
Nonstricturing, nonpenetrating	21 (42.8)
Stricturing	16 (32.6)
Penetrating	12 (24.5)
Localization, <i>n</i> (%)	
L1 terminal ileum	8 (16)
L2 colon	7 (14)
L3 ileocolon	21 (42)
L4 upper	6 (12)
L4 + L3 upper + other	8 (16)
Concurrent immunosuppressant therapy, <i>n</i>	8
Concurrent steroid therapy, <i>n</i>	18
Anti-TNF naïve patients, <i>n</i>	71
Patients with TL < 3 µg/ml, <i>n</i>	43
CD, Crohn's disease; HBI, Harvey-Bradshaw index; TL, trough levels; TNF, tumor necrosis factor; UC, ulcerative colitis.	

Table 2. Promonitor quick ANTI-IFX (whole blood) and promonitor ANTI-IFX ELISA (serum) comparison.

Promonitor Quick ANTI-IFX, n° sample	Promonitor ANTI-IFX ELISA, n° samples		
	Positive	Negative	Total
Positive	13	0	13
Negative	4	83	87
Total	17	83	100
Agreement	(SE) 76.5%	(SP) 100%	
95% CI	56.34–96.66%	–	
Predicted value	(PPV) 100%	(NPV) 95.4%	
95% CI	–	91–99.8%	

CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; IFX, infliximab; NPV, negative predicted value; PPV, positive predicted value; SE, sensitivity; SP, specificity

Table 3. Discrepancies between promonitor quick ANTI-IFX (whole blood) and promonitor ANTI-IFX ELISA (serum): comparison between reference ELISA and POC with serum samples.

Patients	ELISA-ATI (serum)	Index POC test (whole blood)	Repeated POC test (serum) ^a
A	470.8 AU/ml	Negative	Negative
B	61.51 AU/ml	Negative	Positive
C	383.6 AU/ml	Negative	Positive
D	13.66 AU/ml	Negative	Negative

^aSerum stored at or before the index POC test.
ATI, antibody-to-IFX; AU, arbitrary units; ELISA, enzyme-linked immunosorbent assay; IFX, infliximab; POC, point of care.

short-term and long-term therapeutic outcomes in IBD.¹⁶ Proactive Infliximab TDM can efficiently guide therapeutic decisions in different clinical scenarios such as treatment de-escalation,¹⁷ the application of optimized monotherapy instead of combo therapy with immunomodulatory agents,¹⁸ restarting therapy after a long drug holiday,¹⁹ and treatment cessation on deep remission.²⁰

Thus, assessment of drug concentration and anti-drug antibodies is important to help individual dose adjustment and optimize treatment outcome, as shown in several studies carried out in patients on treatment with IFX.^{6–10} However, there are still limitations when applying TDM strategy combined with POC testing for biologic other than IFX. A positive correlation between Adalimumab higher serum concentrations and improved clinical outcome has been reported consistently, and pharmacokinetic studies in CD showed an

increased drug's clearance in the presence of anti-adalimumab antibodies.^{21,22} Currently, the application of Adalimumab TDM into clinical practice is hindered by the lack of adalimumab and anti-adalimumab antibodies threshold interpretation and assay standardization. In a recent study, two POC assays for monitoring Adalimumab concentrations showed a good correlation with ELISA assays. However, adalimumab trough levels measured by POC assays were significantly higher than those obtained by ELISA, and no significant clinical impact compared with empiric dose optimization in case of LOR was shown.²³

Although ELISA tests represent the most commonly used assays for TDM in clinical practice, they are available only in tertiary referral centers. Indeed, ELISA results are not rapidly provided as they require centralization for the analysis due to the need to collect several samples

before proceeding, and the presence of trained laboratory staff. Accordingly, changes in the dosing regimen using ELISA assays can be performed only at the next infusion of the patient, typically 8 weeks later. Thus, POC assays have been developed to provide a qualitative measurement at the patient's bedside, performed by clinical staff without laboratory training, and, ideally, without the need for sample preparation. Moreover, ELISA turnaround time is around 100–200 min whereas time needed for POC testing is much shorter, at around 30 min including serum generation from venous blood, allowing immediate dose optimization based on real-time pharmacokinetic and antidrug-antibodies information. Finally, POC assay allows the possibility of individual testing, without the need for working in series. This would be particularly advantageous in the context of a reactive TDM, with a decision made within the same hospital visit of the patient.

Non-immunologic causes of drug clearance, including high inflammatory burden resulting in rapid drug utilization, and/or excessive drug wasting due to fecal loss, have been described in half of patients with undetectable or sub-therapeutic drug concentrations.²⁴ Interestingly, in our consecutive case series we found that, among patients with sub-therapeutic IFX trough concentrations, 56% of patients demonstrated a double negative status (TL-/ATI-) consistent with a nonimmune-mediated pharmacokinetic failure.

Anti-drug antibodies detection is highly dependent on the assay used and, historically, drug-sensitive assays do not detect anti-drug antibodies in the presence of drug.²⁵ In our pilot study, the absence of ATI in patients with therapeutic and supra-therapeutic TL using POC tests was confirmed in all samples by a drug-tolerant quantitative immunoassay. Altogether, these results support the conclusion that the potential underestimation of ATI led by the presence of free drug is unlikely with the POC kit tested in this study. On the other hand, the main discrepancy observed in our study was the presence of a false negative POC ATI response observed by using whole blood samples. However, whether the direct use of capillary serum could improve POC assay sensitivity should be explored in future studies addressing this issue. An additional limitation of our study relates to the quantitative cut off variability between the two assays, which produces a grey area in patients with antibody levels between

10 AU/ml and 23 AU/ml. However, this intrinsic limitation could be potentially overcome by further development of the POC test and standardization of anti-drug antibody thresholds.

In conclusion, our data suggest that POC measuring ATI can represent a feasible and cost-effective alternative, particularly when the number of samples to test is limited. Despite high specificity, suboptimal sensitivity represents a limitation that should be considered, and ELISA should be performed in doubtful cases with sub-therapeutic drug concentrations. POC for TDM may increase the effectiveness of using TDM to guide therapy in clinical practice, enabling clinicians to immediately perform dose adjustments if needed at the patient's bedside or at the infusion clinic. Nevertheless, this immediate treatment adaptation would be possible only when ATI POC can be combined with IFX TL POC.²⁶

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Author contributions

SF, AB, NA, EVS: involved in study concept and design. SF, RC, NA, DZ: analyzed and interpreted the data, FZ, MDB, LB, MG, BB: performed acquisition of data and critical revision of the manuscript. SF, AB, FZ, EVS: drafted the manuscript, critically revised the manuscript for important intellectual content. FZ, SF: carried out statistical analysis. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethical approval


The study protocol was performed accordingly to the ethical guidelines of the 1964 Declaration of

Helsinki (6th revision, 2008) and approved by the local Ethics Committee (protocol number 3312/AO/14).

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