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ORIGINAL ARTICLE

Performance of a New Rapid Point-of-Care Test for Infliximab Levels in Patients with Inflammatory Bowel Disease: A Comparison to ELISA

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Abstract

Background Therapeutic drug monitoring of infliximab levels in patients with inflammatory bowel disease (IBD) optimizes patients' treatment. The reference technique is based on enzyme-linked immunosorbent assay (ELISA) although point of care (POC) assays are being developed.

Aims To assess the performance of a new rapid immunochromatographic POC assay (Promonitor Quick IFX) compared with ELISA technique to measure infliximab levels in patients with IBD.

Methods A prospective, observational, unicentric study was performed on capillary blood samples from patients with IBD before infliximab infusion (trough levels). Infliximab levels and anti-infliximab antibodies were measured using the ELISA technique (Promonitor IFX) and the POC assay. Correlation between both techniques was assessed by Pearson's coefficient. Quantitative differences were evaluated by Bland–Altman analysis. Samples were stratified according to infliximab therapeutic ranges (< 3 µg/mL, 3–8 µg/mL, and > 8 µg/mL).

Results A total of 135 experimental samples were assessed. Infliximab levels showed a high correlation between POC and ELISA tests ($r = 0.84$, $P < 0.001$). The mean difference between tests was 1.46 µg/mL ($P < 0.001$), being minimal for concentrations < 8 µg/mL. POC and ELISA assays showed an overall concordance of 87.4%. Most samples were in the same therapeutic range, which lead to equivalent therapeutic decisions. POC and ELISA assays detected the presence of anti-infliximab antibodies in 2.2% and 3.7% of the samples, respectively.

Conclusions POC assay results in blood samples from patients with IBD were comparable to those obtained with the reference ELISA technique. The POC assay could be considered for routine testing based on its ease of use and rapidity.

Keywords ELISA · Point-of-care · Therapeutic drug monitoring · Infliximab · Inflammatory bowel disease

Introduction

Infliximab is a chimeric monoclonal antibody against tumor necrosis factor-α (anti-TNF) which has proven to be an effective treatment for several chronic immune-mediated inflammatory disorders [1]. Specifically, for inflammatory bowel disease (IBD), infliximab reduces disease-associated symptoms, hospitalization rates, prevents surgical procedures and improves health-related quality of life [2, 3]. Although anti-TNF therapy is highly effective, several mechanisms may affect drug pharmacokinetics such as the presence of anti-infliximab antibodies, a low serum albumin concentration, high body mass index and the concomitant treatment with immunosuppressors [4, 5].

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Therapeutic drug monitoring (TDM) of anti-TNF agents is a well-established tool to optimize biological therapies in patients with IBD. TDM measures drug levels (e.g., infliximab) and anti-drug antibodies to achieve the maximum clinical benefit [6]. The use of TDM in patients with IBD under treatment with infliximab is associated with a better clinical response [7, 8]. Moreover, a systematic review evidenced that TDM is cost-effective in IBD, without impact on clinical efficacy [9]. Several therapeutic ranges and cut-offs have been proposed to assess the clinically relevant drug concentrations associated with improved clinical outcome in IBD [10, 11]. Altogether, TDM has the potential to improve the efficacy and safety of biological therapies, and allows individually tailored decision making, by optimizing serum drug levels within a therapeutic range [12].

To date, several laboratory techniques have been developed and validated to quantify serum infliximab concentration and anti-infliximab antibodies, such as enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, high mobility shift assay, and gene reporter assay [13]. Of these, the most common technique used is based on ELISA, which is sensitive, specific and inexpensive [14]. Comparability studies between ELISA tests have shown a high level of correlation [15]. The main limitation of ELISA-based testing is that requires several samples to be accumulated to reduce the cost of each determination before sending them out to a centralized laboratory.

Point-of-care (POC) assays are rapid tests with quick turnaround times and with a specificity equivalent to the gold-standard technique ELISA, which are being developed to inform clinical decisions in a timely manner [16]. Hence, the increasing use of TDM as a clinical decision tool reveals the importance of the availability of POC tests, which may overcome limitations of ELISA-based testing [17, 18]. In patients with IBD treated with infliximab, POC tests have been used during routine clinical practice to detect anti-infliximab antibodies [19, 20].

To date, a limited number of studies have compared POC and ELISA techniques in terms of effectiveness and robustness to monitor infliximab levels in IBD [18, 21, 22]. In this context, this study offers new insights and benefits of a recently developed POC test in patients with IBD treated with infliximab.

Methods

Study Aim

This was a prospective, observational, unicentric study aimed to evaluate the performance of a rapid POC test (Promonitor Quick IFX and Promonitor Quick anti-IFX; Progenika Biopharma, a Grifols company; Derio; Spain) to measure infliximab and anti-infliximab levels, respectively, in samples from patients with IBD, in comparison to the ELISA reference techniques (Promonitor IFX and Promonitor anti-IFX; Progenika Biopharma). The study was conducted at the Digestive System department of the University Hospital Virgen Macarena (Spain). The protocol was reviewed and approved by the Institutional Review Board / Independent Ethics Committee (CEIm Provincial Sevilla, Spain) in July 29, 2021. The study was conducted in full conformity with appropriate local laws and regulations and the Declaration of Helsinki.

Sampling

Blood samples were obtained between July 2021 to December 2021 from consecutive patients diagnosed with IBD (Crohn's disease or ulcerative colitis), older than 18 years old, and under treatment with infliximab during induction phase (week 6 and 14) and maintenance phase (one year of treatment). Data were recorded in electronic case report forms. All patients signed the written informed consent before study initiation.

Blood samples were collected prior infliximab infusion (trough levels). Infliximab levels were measured in finger prick samples with Promonitor Quick IFX, and simultaneously in peripheral blood samples with Promonitor IFX.

Determination of Infliximab Levels

The Promonitor Quick IFX is a rapid POC immunochromatography assay for the quantitative detection of infliximab levels based on lateral flow technology in capillary whole blood or serum, with a lower and higher limit of quantification in blood between 1.1 and 58 µg/mL. The test was taken during the visit and results in µg/mL were available after 20 min. A therapeutic decision (increase, maintain, or lowering infliximab dose) was taken during the same visit. Promonitor Quick IFX test is standardized with the WHO international standard for infliximab, demonstrating comparable results between the POC test and the true value of the international standard [23].

Promonitor IFX is an ELISA-based test to monitor infliximab levels in patients with biological therapy for the treatment of chronic inflammatory diseases, with a range of detection between 0.035 and 14.4 µg/mL. Serum samples assessed by ELISA method were measured at the hospital pharmacy laboratory and result was typically available after two weeks. A therapeutic decision was delayed after the appointment of a new visit.

Determination of Anti-infliximab Antibodies

When infliximab levels were below the limit of quantitation (1.1 µg/mL) using the POC Promonitor Quick IFX assay, anti-infliximab antibodies were assessed with the Promonitor Quick anti-IFX assay (also a POC device). A qualitative result (presence / absence) was available in 30 min. Therefore, a therapeutic decision was taken during the same visit.

When infliximab levels were < 0.3 µg/mL using the ELISA Promonitor Quick IFX assay, anti-infliximab antibodies were assessed with the ELISA-based Promonitor anti-IFX assay, which provides results in U/mL (arbitrary units). As it happened with the Promonitor IFX test, the therapeutic decision was delayed until results were released by the hospital pharmacy laboratory and a new visit was appointed.

Data Analysis

Considering an alpha = 0.05, a power of 80%, and a mean proportion of 82.5%, a sample size of at least 99 blood specimens was needed to detect a 15% of difference between both tests.

Continuous variables were expressed using the median and interquartile range. The correlation between both assays was assessed using the Pearson correlation coefficient (r). Quantitative comparison of both assays included mean (SD) and 95% CI (mean ± 1.96*SD), which was plotted by the difference of their mean for each sample using Bland–Altman Plots and analyzed by Student's t-test.

Qualitative comparison between POC and ELISA tests was analyzed by the kappa coefficient, after stratifying samples by sub-, normal, and supra-therapeutic ranges of infliximab levels (< 3 µg/mL, 3 to 8 µg/mL, and > 8 µg/mL, respectively) as referred to in previous research [10, 24]. Statistical significance was set as a p-value of < 0.05. Statistical analyses were performed using the R® software version 4.1.2 (R Core Team, Vienna, Austria).

Results

Infliximab Levels

A total of 135 blood samples were assessed. The overall infliximab concentration was 3.90 (2.00–6.25) µg/mL using the rapid POC test, and 5.09 (2.83–8.20) µg/mL (median and interquartile range), using the ELISA test. The correlation between infliximab concentrations measured by POC and ELISA assays was high ($r = 0.84$, $P < 0.001$). The slope was 0.68, and an intercept was 0.478 (Fig. 1). Despite the apparent higher variability in infliximab concentrations above 10 µg/mL as measured by ELISA, correlation for this subset was still significant ($r = 0.59$, $P = 0.0024$).

The Bland–Altman analysis showed that the mean infliximab concentration difference between POC test

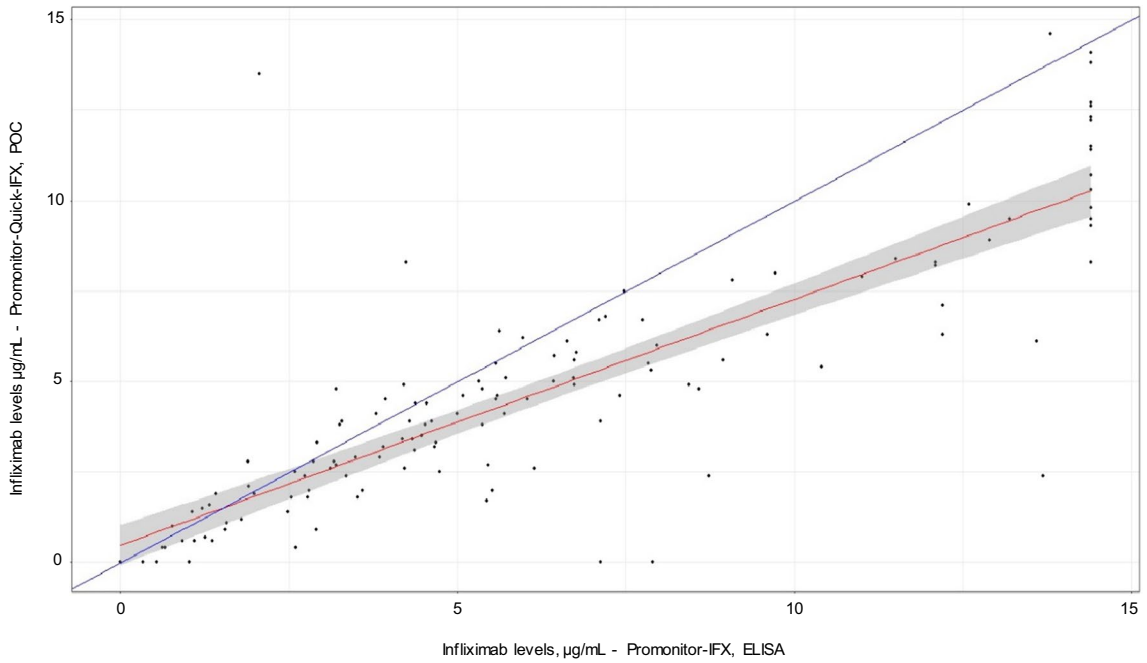

Fig. 1 Correlation between infliximab concentrations (µg/mL) measured by Promonitor Quick IFX point-of-care (POC) and Promonitor IFX ELISA tests. Identity line (y = x) is represented in blue. Red line is the regression curve (y = 0.68x + 0.478). Grey shaded band represent the 95% confidence intervals. Pearson correlation coefficient, $r = 0.84$, $P < 0.001$

and ELISA test was 1.46 µg/mL ($P < 0.001$). Although the POC test tended to slightly underestimate infliximab concentration for values above 8 µg/mL in ELISA, differences between both assays were minimal for infliximab concentrations below 8 µg/mL (Fig. 2). However, there were overall few values outside the 95% CI and most of them were widely distributed across all range of concentrations.

Therapeutic Ranges

Samples were stratified by therapeutic ranges of infliximab levels. Distribution of samples according to concordance between the POC and ELISA assays is shown in Table 1. Overall, the kappa value was 0.84. POC method results were overall concordant with ELISA test results in 87.4% (118/135) patients. In those patients with infliximab levels < 3 µg/mL, a 69.8% (37/53) of agreement was observed. In those samples with infliximab levels between 3 and 8 µg/mL the agreement achieved 98.1% (53/54). In patients with infliximab levels > 8 µg/mL the concordance level was 100% (28/28).

Table 1 Distribution of samples according to concordance between the Promonitor Quick IFX point-of-care (POC) and Promonitor IFX ELISA assays, when infliximab levels were stratified by therapeutic range (< 3 µg/mL; 3–8 µg/mL; > 8 µg/mL)

Promonitor Quick IFX (POC)	Promonitor IFX (ELISA)			
	< 3 µg/mL	3–8 µg/mL	> 8 µg/mL	Total
< 3 µg/mL	37	0	0	37
3–8 µg/mL	16	53	0	69
> 8 µg/mL	0	1	28	29
Total	53	54	28	135

ELISA enzyme-linked immunosorbent assay; *POC* point of care

Anti-infliximab Antibody Levels

The POC test detected infliximab levels below the threshold of detection (1.1 µg/mL) in 3 samples (2.2%), in which the presence of anti-infliximab antibodies was confirmed.

With the ELISA test, 5 samples (3.7%) showed low infliximab levels of < 0.3 µg/mL. Levels of antibodies against infliximab detected with the Promonitor anti-IFX assay in those samples were: 7.51 U/mL, 19.7 U/mL, < 2 U/mL, 68 U/mL, and 3.27 U/mL.

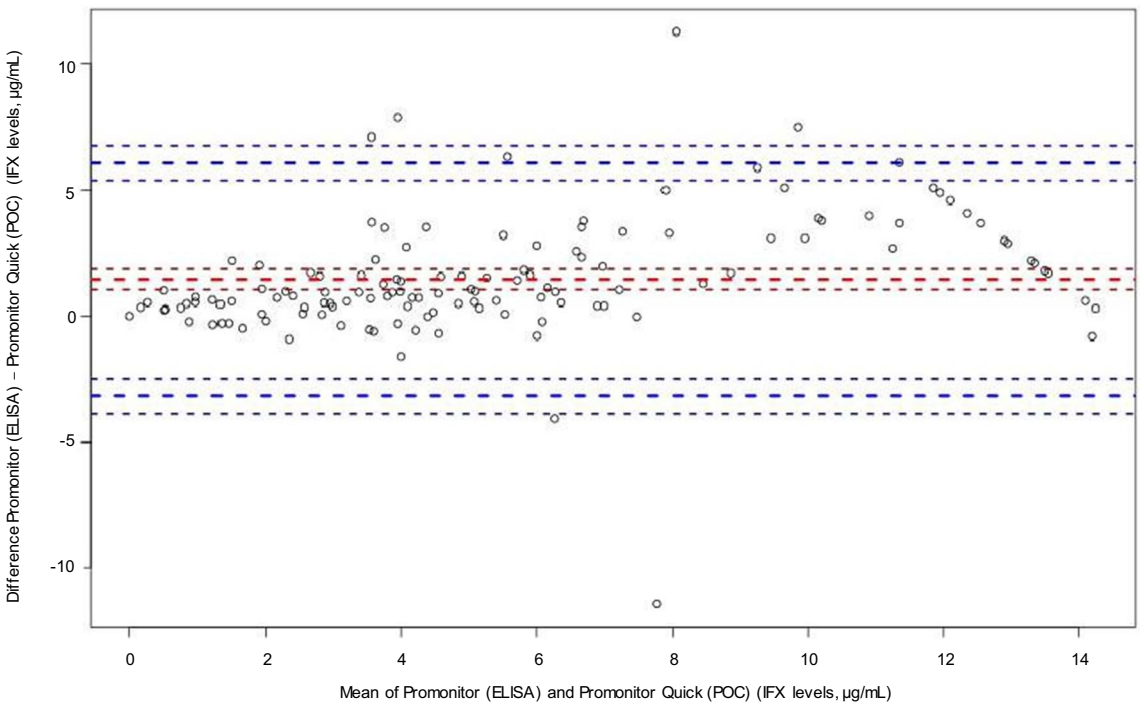

Fig. 2 Bland–Altman plot of absolute difference of infliximab concentrations (µg/mL) measured with the Promonitor Quick IFX point-of-care (POC) and Promonitor IFX ELISA assays plotted against mean IFX concentration. Dashed red line indicates mean difference of infliximab between ELISA and POC test (1.46 µg/mL). Dashed blue lines represent the upper and lower 95% confidence interval

Discussion

The assessment of clinical agreement is paramount when comparing drug levels between different analytical methods. The present study assessed the performance of the rapid POC tests Promonitor Quick IFX and Promonitor Quick anti-IFX in comparison with the reference ELISA tests Promonitor IFX and Promonitor anti-IFX assay, in samples from patients with IBD under treatment with infliximab as an aid for TDM. The results showed a high degree of agreement between both tests. A high level of agreement was also confirmed when samples were stratified by therapeutic ranges of infliximab levels.

The high level of correlation between POC and ELISA techniques ($r = 0.84$), demonstrated that POC assay was reliable to determine infliximab levels in patients with IBD. The correlation levels between both assays was comparable to that reported in previous studies where POC and ELISA tests were compared [18, 21, 22]. Similarly, a recent study showed a good correlation ($r = 0.85$) between POC and ELISA to measure infliximab and anti-infliximab in patients with rheumatoid arthritis [25]. It is reasonable to presume that the use of POC testing may also be extrapolated to other chronic immune-mediated inflammatory disorders, where infliximab is indicated as a therapeutic agent [26].

When the mean absolute difference between both methods was compared, the mean bias of Promonitor IFX ELISA assay was higher than that of Promonitor Quick IFX POC test. While the findings of the present study are in agreement with other studies in which ELISA tests showed higher infliximab levels than POC assays [22], the opposite results have also been reported [27]. There were minor differences between both assays at low concentrations (< 8 µg/mL), which is the most interesting range from a clinical perspective. Conversely, at concentrations higher than 8 µg/mL, the POC test underestimated infliximab levels. This was not unexpected considering previous studies, in which the scattering of the values increased in samples with higher infliximab levels [17, 22]. Importantly, the risk of underestimating high infliximab levels may be relevant for the pediatric populations where levels are often kept well above 10 µg/mL, and even above 12.5 µg/mL in patients with more refractory disease [28]. This presents an opportunity for the development of better POC assays that can more accurately detect high infliximab levels.

Overall, the kappa value was high, which suggests a good agreement between both methods. Remarkably, this study revealed that most samples were in the same therapeutic range group when measuring infliximab levels by the ELISA and the POC assays, with an overall concordance of 87.4%, therefore leading to equivalent therapeutic decision. This is important, considering that the goal of TDM is to determine drug levels and antibodies to improve the management of patients with IBD by guiding clinical decisions such as dose optimization (increase, maintain or decrease drug dose), interval optimization or switching to another TNF-α inhibitor [6, 29].

In contrast to older POC tests, which required serum instead of whole blood [30], Promonitor Quick IFX directly analyzes capillary whole blood using finger prick samples, thus providing results in only 20 min [31]. This allowed that results were obtained individually for each patient at the infusion center, without the need of batch sampling before processing as required by ELISA tests. This rapid approach facilitated TDM and supported immediate informed decision, without waiting until the following visit to optimize the drug dose. As previously suggested [32], obtaining real-time results and targeting adequate drug concentrations would increase the effectiveness of TDM and may represent a viable strategy to prevent loss of response to biologic agents.

In a pilot study, Promonitor Quick anti-IFX test demonstrated a good agreement with the ELISA-based test to detect anti-infliximab antibodies with a smaller cohort of patients with IBD [19]. In our study, in the few samples with low infliximab levels the Promonitor IFX ELISA detected two more than the Promonitor Quick IFX POC, as it could be expected from its lower threshold of detection (0.3 µg/mL vs. 1.1 µg/mL, respectively). However, in TDM, since the evolution of drug levels is that relevant to make a therapeutic decision, the advantage provided by the POC assay of having almost immediate results largely exceeds the slightly better sensitivity of the ELISA assay.

Limitations of the study should be acknowledged. The study was unicentric, thus limiting the external validity of the results and the assessment of reproducibility between sites. The study assessed the performance of the POC in blood samples, not the resulting therapeutic decisions in the patients who donated the samples. In addition, we assessed a relatively small number of samples, although the tested cases covered a broad range of drug concentrations. Finally, only Promonitor ELISA assays were used for comparison. However, Promonitor ELISA results for infliximab levels have been shown comparable to other ELISA assays [33–35].

In conclusion, the present study demonstrated that Promonitor Quick IFX was reliable to quantify infliximab levels in capillary blood samples from patients with IBD and results were comparable to those obtained with the reference ELISA technique. Our results, combined with the known ease of use and rapidity of the POC assays, suggest that Promonitor Quick IFX could be used as a routine test in clinical practice.

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Author's contribution Conceptualization: FA-A; Data curation: TV-D, FA-A, AA-P, VM-B, JM-M, and MMA; Formal analysis: TV-D, FA-A, AA-P, VM-B, JM-M, and MMA; Investigation: TV-D, FA-A, AA-P, VM-B, JM-M, and MMA; Validation: BM, MB and BB; Visualization: BM, MB and BB; Supervision: LC, AC and MAC; Project administration: LC, AC and MAC; Writing – Review and Editing: TV-D, FA-A. Approval of the final manuscript: all authors.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest F. Argüelles-Arias, B. Maldonado, L. Castro, M. Belvis, B. Benítez, and Á. Caunedo, have served as speaker, consultant, and advisory member for, or has received research funding from: MSD, Abbvie, Pfizer, Kern Pharma, Takeda, Janssen, Ferring, Faes Farma, Shire Pharmaceuticals, Tillotts Pharma, Galápagos and Chiesi. T. Valdés-Delgado has served as speaker, consultant, and advisory member for, or has received research funding from: Janssen, Tillotts Pharma, and Galapagos. V. Merino-Bohórquez has served as speaker, consultant, and advisory member for, or has received research funding from: Janssen, Abbvie, Kern Pharma, Pfizer, Sandoz, Novartis, and Galapagos. J. Martín-Manzanares, M.M. Alonso, A. Aguado-Paredes, and M.A. Calleja have no conflict of interest.

Ethical approval The study protocol was reviewed and approved by the Institutional Review board/ Independent Ethics Committee of Research with Medicines (CEIm) Provincial of Seville. All patients signed the written informed consent before study initiation.

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