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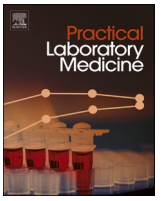

Detection of infliximab, adalimumab, and anti-drug antibodies: Development and validation of new monotest, automated assays on multiparametric instrument

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ABSTRACT

Objective: To convert manual ELISA kits to fully automated immunoassays that quantify serum drug levels and anti-drug antibodies levels of infliximab and adalimumab (CHORUS Promonitor kits).

Desing and methods: CHORUS Promonitor INFLIXIMAB, CHORUS Promonitor ADALIMUMAB, CHORUS Promonitor ANTI-INFLIXIMAB, and CHORUS Promonitor ANTI-ADALIMUMAB kits were compared with the corresponding Promonitor kits to determine sensitivity and specificity of the assays. For the automated assays, the entire procedure -from samples dilution to final readouts-was performed by CHORUS TRIO instrument (DIESSE, Italy). Residual human serum samples from clinical laboratory investigations and samples resulting from the addition of specific drugs (IFX or ADL) or anti-drug antibodies (anti-IFX or anti-ADL) were used for the characterization and validation of the tests.

Results: CHORUS Promonitor kits showed an excellent agreement (Cohen's coefficient = 1) with the Promonitor kits and were linear within predefined ranges. All assays were accurate and repeatable, as an acceptable variability were observed within runs, between runs, lots, and instruments. No difference in detecting the reference drug or biosimilars emerged.

Conclusion: During preclinical development, these kits resulted as sensitive, specific, accurate, and able to quantify either the reference drug or the corresponding biosimilars. All these features support their use in clinical practice for therapeutic drug monitoring of patients with inflammatory diseases under treatment with IFX or ADL.

1. Introduction

The anti-tumor necrosis factor alpha (TNFα) agents infliximab (IFX) and adalimumab (ADL) are currently used to manage several inflammatory diseases, including psoriasis, rheumatoid arthritis, Chron disease, inflammatory bowel disease. Although the use to anti-TNFα is effective and well established, almost 30% of patients fail to respond showing primary resistance to the treatment and 50% lose

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the response after a few months for secondary resistance [1,2].

Nearly half of patients with rheumatoid arthritis treated with IFX developed anti-IFX antibodies within the first year of treatment [2,3]. Similarly, in patients with moderate-to-severe psoriasis, anti-IFX antibodies are thought to be responsible for the loss of response and infusion reactions during IFX treatment, thus determining decreased adherence to treatment [4].

Long-term treatment with ADL over 3 years determined the development of anti-drug antibodies that led to lower ADL concentration and a lower likelihood of minimal disease activity or clinical remission [5]. Anti-drug antibodies against ADL were detected also in patients with plaque psoriasis with reduced serum ADL trough concentrations and non-response or loss of response to the therapy [6].

The lack of response may be attributed to both a sub-therapeutic drug concentration and anti-drug antibodies development. The response in terms of the durability of drug therapy, reduction of antibody formation risk, severe infusion reactions, and decrease in hospitalisations, can be improved by the therapeutic drug monitoring (TDM) of blood drug concentrations, as well as TDM has been the most promising approach for treating secondary anti-TNF drug failure [7].

Several assays are available on the market to measure IFX and ADL trough levels and related anti-drug antibodies (ADAs); of these, the enzyme-linked immunosorbent assay (ELISA), the radioimmunoassay (RIA), and the homogenous mobility shift assay (HMSA) are the three most used. Currently, the solid phase assay (ELISA) is the only technique that can be used for the TDM of all TNF inhibitors as well as for the quantitative investigation of ADAs, resulting in the gold standard technology [7].

This work described the development of four fully automated immunoassays that quantify serum through drug levels and anti-drug antibodies levels of IFX and ADL in plasma patients. The main goal was to convert manual ELISA kits in the automated corresponding platform (CHORUS). Data on the ability of these assays to detect biosimilars of IFX and ADL were also presented.

2. Material and methods

2.1. Principles of the immunoassays

Four fully automated immunoassay kits were developed in collaboration with Progenika Biopharma, a Grifols company (Bilbao, Spain) to determine the concentration of IFX and ADL and their anti-drug antibodies in human serum.

CHORUS Promonitor INFLIXIMAB kit was an ELISA quantitative assay, CHORUS Promonitor ADALIMUMAB was a sandwich ELISA, whereas CHORUS Promonitor ANTI-INFLIXIMAB and CHORUS Promonitor ANTI-ADALIMUMAB kits were semiquantitative assays based on bridging ELISA. Bridging ELISA is a specific type of sandwich ELISA, where a dimeric or oligomeric antigen (usually an antibody within a sample) is detected utilizing both a capture and a detection antibody. The antigen acts as a bridge between the two specific antibodies. According to the manufacturer's instructions, in the IFX capture ELISA method, the microwell strips were pre-coated with an anti-TNF-alpha human monoclonal antibody bound to human recombinant TNF-alpha. IFX present in human serum sample bound to pre-immobilized TNF-alpha following an incubation step. A second horseradish peroxidase (HRP)-labelled anti-IFX antibody (conjugate) bound to the IFX already attached to the microwells. After washing away the excess unbound conjugate and adding a chromogenic substrate, the intensity of the colour developed was measured through a spectrophotometric reading.

The sandwich ELISA works similarly to the capture ELISA but in this case, the microwell strips are pre-coated with anti-ADL antibody to detect ADL present in the human serum tested. The same principle underlies the bridging assays to detect anti-drugs, using microwell strips pre-coated with its specific drug.

CHORUS Promonitor INFLIXIMAB, CHORUS Promonitor ADALIMUMAB, CHORUS Promonitor ANTI-INFLIXIMAB, and CHORUS Promonitor ANTI-ADALIMUMAB kits are produced by DIESSE (Italy). The kits consist of 36 ready-to-use devices and contain all reagents required for the detection of IFX or ADL and their anti-antibodies, including a calibrator and a positive control for internal validation.

All readouts were performed with CHORUS TRIO instrument, a fully automated system developed by DIESSE Diagnostica Senese SpA Società Benefit. CHORUS TRIO is a multiparametric diagnostic instrument capable of simultaneously performing a wide range of tests for both infectious and autoimmune diseases. It uses devices containing ready-to-use reagents and conducts all operations from sample processing to printing the report in automated manner. The operator manually dispenses the serum sample into the device, and the instrument independently performs the ELISA steps. The instrument can simultaneously analyze 30 samples; it can provide both qualitative (positive/negative) and quantitative (ng/mL, IU/L, etc.) results.

2.2. Validation

Residual human serum samples from clinical laboratory investigations and samples resulting from the addition of specific drugs (IFX or ADL) or anti-drug antibodies (anti-IFX or anti-ADL) were used for the characterization and validation of the tests.

As all samples had been anonymized after discard, this study did not require an informed consent. The study was conducted according to the ethical principles reported in the Declaration of Helsinki in its latest revision.

To determine the diagnostic sensitivity and specificity of the assays, the CHORUS Promonitor kits (test methods) were compared to the corresponding Promonitor (Grifols) kits (predicate device). All reagents used of the automated kits were identical to those of manual kits, and both tests were run at the same time after thawing.

The level of agreement between CHORUS Promonitor and Promonitor kits was determined by Cohen's coefficient. Passing Bablock and Spearman coefficient were also calculated. The serum sample was considered negative when IFX or ADL concentration was lower than 0.3 μg/mL, while in the case of anti-drug antibodies, negative samples were $\leq$ 5 AU/mL for anti-IFX and $\leq$ 10 AU/mL for anti-

ADL.

Linearity was assessed by testing ten serial dilutions of 3 samples, at known concentration, in duplicate, in order to cover the whole calibration range; the accuracy was tested with the first International Standard for IFX [NIBSC code: 16/170; National Institute for Biological Standards and Control, Hertfordshire, United Kingdom [8]] or the first International Standard for ADL [NIBS Code: 16/236, National Institute for Biological Standards and Control, Hertfordshire, United Kingdom [9]].

Precision and repeatability were assayed by using 6 samples at different concentrations. For intra-assay precision, the analysis was performed with one lot of the kit on one CHORUS instrument. Each analyte concentration was tested in 6 replicates. For the inter-assay precision, each analyte concentration was tested over 6 runs. The inter-lot precision was evaluated with 3 lots of the kit on one CHORUS TRIO instrument and each of the 6 samples is tested in duplicate; the inter-instrument precision was analysed with 1 lot of the kit on 3 CHORUS TRIO instruments and each sample was tested over 6 runs with the 3 instruments. In all experiments, one control sample was added to judge the acceptability of the run. A coefficient of variability (CV) $\leq$15% was accepted.

The Limit of Detection (LoD) and the Limit of Lower and Upper Quantitation (LloD and UloD) was measured according to the EP17-A2 approved guideline second edition CLSI (Clinical and Laboratory Standards Institute), setting the accuracy goal at 15% [10]. Limits of detection of each kit are available in manufacturer's instructions.

2.3. Quantification of biosimilar drugs

A bias evaluation study was performed to test the ability of the CHORUS Promonitor INFLIXIMAB device to quantify some commercially available biosimilar drugs [Remsima® (Celltrion Health Care, Incheon, South Korea), Flixabi™ (Samsung Bioepis, Incheon, South Korea), Zessly®(Sandoz GmbH, Bavaria, Germany)], compared to the reference drug (Remicade®, MSD, Kenilworth, NJ, USA). Similarly, Humira® (Abbvie, North Chicago, IL, USA) was used as a comparator to test biosimilar Amgevita® (Amgen, Thousand Oaks, CA, USA) and Imraldi® (Biogen, Cambridge, MA, USA) in the CHORUS Promonitor ADALIMUMAB device. Each sample was spiked with the reference brand and biosimilar drugs and tested in triplicate for 6 days. The test was performed according to the manufacturer's instructions. The mean of the obtained values was calculated and the bias between the reference brand and

Table 1
Comparison between CHORUS Promonitor and Promonitor ELISA predicate
(A) Comparison between CHORUS Promonitor INFLIXIMAB (test) and Promonitor-IFX (predicate); **(B)** Comparison between CHORUS Promonitor ADALIMUMAB and Promonitor-ADL (predicate); + indicates positive samples, - indicates negative samples (<0.3 μg/mL); **(C)** Comparison between CHORUS Promonitor ANTI-INFLIXIMAB (test) and Promonitor-ANTI-IFX (predicate), **(D)** Comparison between CHORUS Promonitor ANTI-ADALIMUMAB and Promonitor-ANTI-ADL; + indicates positive samples, - indicates negative samples ($\leq$5 AU/mL for anti-IFX and $\leq$ 10 AU/mL for anti-ADL).

A				
		Predicate		
		+	–	Total
Test	+	50	0	50
	–	0	115	115
	Total	50	115	165

B				
		Predicate		
		+	–	Total
Test	+	47	0	47
	–	0	106	106
	Total	47	106	153

C				
		Predicate		
		+	–	Total
Test	+	32	0	32
	–	0	124	124
	Total	32	124	156

D				
		Predicate		
		+	–	Total
Test	+	44	1	45
	–	0	123	123
	Total	44	124	168

k Cohen's coefficient = 1 (excellent agreement).
k Cohen's coefficient = 0.97 (excellent agreement).

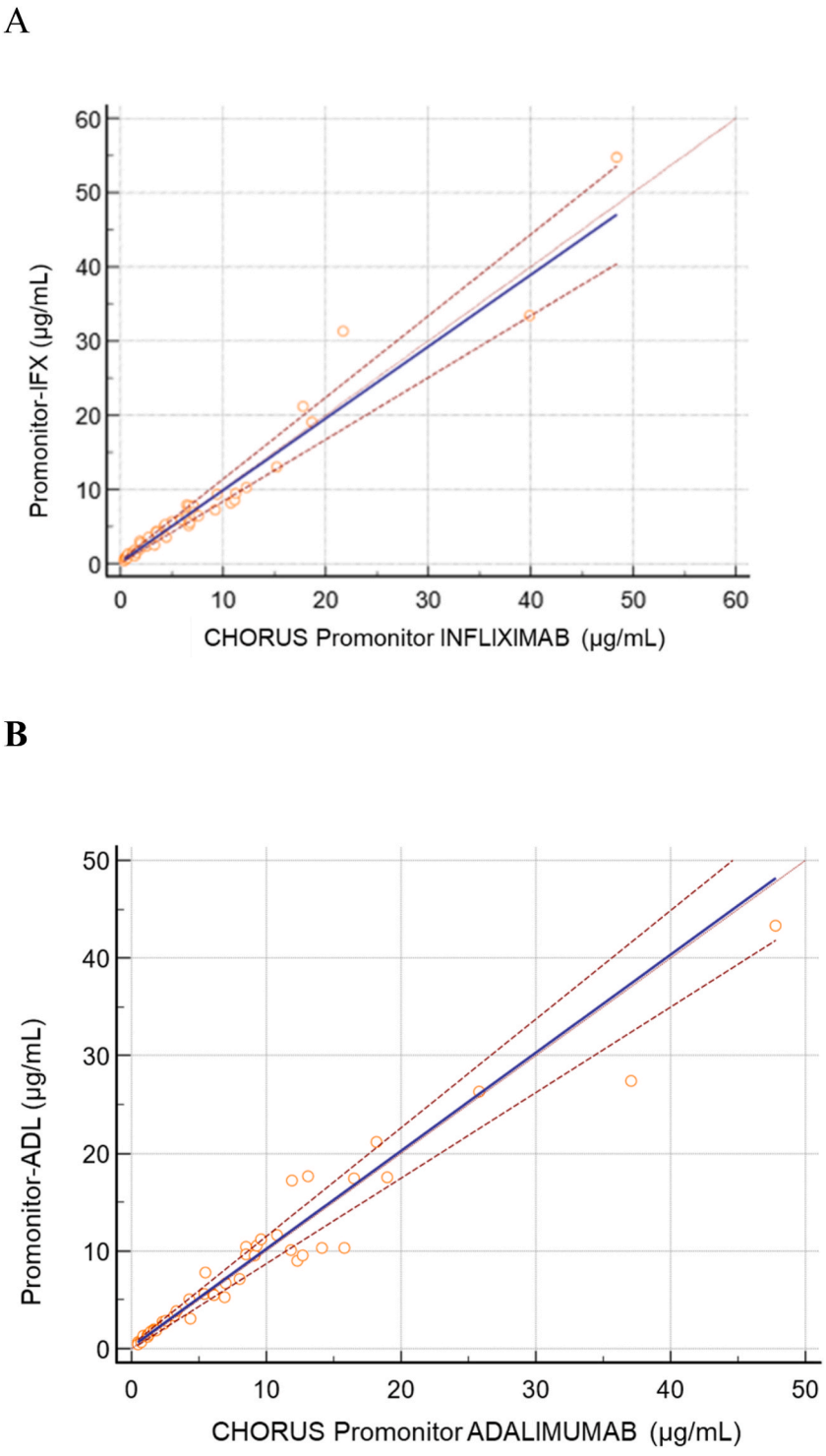

Fig. 1. **(A)** Passing Bablock regression of CHORUS Promonitor INFLIXIMAB (test method) versus Promonitor-IFX (predicate device) Intercept 0.186 (95% CI 0.043 to 0.400), Slope 0.968 (95% CI 0.834 to 1.099). Spearman's Correlation: r = 0.984, 95% CI: 0.972 to 0.99. **(B)** Passing Bablock regression of CHORUS Promonitor ADALIMUMAB (test method) versus Promonitor-ADL (predicate device) Intercept −0.200 (95% CI -0.425 to 0.050), Slope 1.000 (95% CI 0.899 to 1.141). Spearman correlation: r = 0.974, 95% CI: 0.954 to 0.986.

biosimilar drugs was estimated for each level, according to CLSI EP10-A3 Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures [11].

3. Results

3.1. Diagnostic sensitivity and specificity

One hundred sixty-five human serum samples were tested with CHORUS Promonitor INFLIXIMAB and Promonitor-IFX ELISA kits to assess diagnostic sensitivity and specificity: 50 samples were positive with both kits and 115 samples were negative. The overall percent agreement between the test method and the predicate device was 100% (95% CI 97.7–100.0) and Cohen's coefficient was 1, showing an excellent agreement (Table 1A). Only positive samples were included in the Passing Bablock analysis, since all the tested negative samples were undetectable, (detection range ≥0,3 μg/ml). A high correlation was observed between the two assays (Fig. 1A).

CHORUS Promonitor ADALIMUMAB and Promonitor-ADL kits were compared with 153 human serum samples of which 47 resulted to be positive and 106 were negative. Also in this case, the agreement was excellent with a Cohen's coefficient 1 (Table 1B) and the correlation between the test method and predicate device was high (Fig. 1B).

CHORUS Promonitor ANTI-INFLIXIMAB and CHORUS Promonitor ANTI-ADALIMUMAB were compared with Promonitor anti-IFX and Promonitor anti-ADL on 156 and 168 serum samples, respectively. In both cases, the level of agreement between the test method and the predicate was excellent (Cohen's coefficient 1 and 0.97, respectively. Table 1; C, D). Passing Bablock regression was also performed and the results were summarised in Supplementary Fig. 1. Spearman's Correlation was r = 0.984, 95% CI: 0.972 to 0.99 between CHORUS Promonitor INFLIXIMAB versus Promonitor-IFX and r = 0.974, 95% CI: 0.954 to 0.986 between CHORUS Promonitor ADALIMUMAB versus Promonitor-ADL.

3.2. Linearity and accuracy

CHORUS Promonitor INFLIXIMAB kit was tested with the first International Standard for IFX to assess the accuracy and linearity. The linearity ranged from 0.42 μg/mL to 25.0 μg/mL and was extended from 0.37 μg/mL to 48.9 μg/mL by testing two additional highly positive samples (Supplementary Fig. 2A). The linearity of the CHORUS Promonitor ADALIMUMAB kit, assessed with the First International Standard for ADL, was confirmed with serial dilutions of 2 other serum samples at a known concentration and ranged from 0.34 μg/mL to 55.0 μg/mL (Supplementary Fig. 2B).

CHORUS Promonitor ANTI-INFLIXIMAB kit was linear from 2.3 AU/mL to 1422.7 AU/mL, whereas CHORUS Promonitor ANTI-ADALIMUM AB kit was linear from 6.8 AU/mL to 1650.0 AU/mL (Supplementary Figs. 2C and D).

Data on precision and repeatability were summarised in Supplementary Table 1.

3.3. Quantification of biosimilars

The ability of CHORUS Promonitor devices to quantify biosimilar IFX and ADL drugs is summarised in Table 2. Both CHORUS Promonitor INFLIXIMAB and CHORUS Promonitor ADALIMUMAB could detect all IFX and ADL commercially available biosimilars, respectively, with low bias.

Table 2
Biosimilar quantification with CHORUS Promonitor
(A) Infliximab biosimilar quantification. The spiking initial concentrations were 24.5 (level 1), 12.3 (level 2), 5.5 (level 3) μg/mL. Three concentrations of the IFX originator drug and biosimilars were quantified with CHORUS Promonitor INFLIXIMAB assay; the bias indicates the difference between the measurements of biosimilar and originator drug. **(B)** Adalimumab biosimilar quantification. The spiking initial concentrations were 33.7 (level 1), 17.8 (level 2), 9.3 (level 3) μg. Three concentrations of the ADL originator drug and biosimilars were quantified with CHORUS Promonitor ADALIMUMAB assay; the bias indicates the difference between the measurements of biosimilar and originator drug.

A

	CHORUS Promonitor INFLIXIMAB		
	Level 1	Level 2	Level 3
Mean reference IFX (Remicade®)	24.5 μg/mL	12.0 μg/mL	5.6 μg/mL
Remsima® (Bias Remsima®-Remicade®)	32.6 μg/mL (8.1)	13.9 μg/mL (1.6)	6.5 μg/mL (1.0)
Flixabi™ (Bias Flixabi™-Remicade®)	29.5 μg/mL (5.0)	14.9 μg/mL (2.6)	7.4 μg/mL (1.9)
Zessly® (Bias Zessly®-Remicade®)	24.9 μg/mL (0.4)	10.9 μg/mL (−1.4)	6.3 μg/mL (0.8)
	CHORUS Promonitor ADALIMUMAB		
	Level 1	Level 2	Level 3
Mean reference ADL (Humira®)	35.4 μg/mL	18.6 μg/mL	9.8 μg/mL
Amgevita® (Bias Amgevita®-Humira®)	33.2 μg/mL (−2,2)	16.7 μg/mL (−1,9)	8.5 μg/mL (−1,3)
Imraldi® (Bias Imraldi®-Humira®)	33.0 μg/mL (−0,7)	18.5 μg/mL (0,7)	8.4 μg/mL (−0,9)

4. Discussion

In this work, four CHORUS Promonitor kits were tested to determine their diagnostic sensitivity, specificity, linearity, accuracy, and, in the case of CHORUS Promonitor INFLIXIMAB and CHORUS Promonitor ADALIMUMAB, also the ability to quantify commercially available IFX and ADL biosimilars.

All CHORUS Promonitor devices presented the similar diagnostic sensitivity and specificity as the predicate Promonitor assays. Indeed, only one serum showed discordant tests interpretation, because its concentration felt within a borderline zone. According to the Food and Drug Administration guidelines [12], sensitivity is defined as the lowest concentration at which the antibody preparation consistently produces a positive result and specificity refers to the ability of a method to exclusively detect the target analyte. Therefore, the excellent agreement with predicate devices to distinguish positive and negative serum samples provides some indication of the ability of CHORUS Promonitor kits to avoid false-positive or false-negative results. The analysis of the International Standard also showed correspondence, although it is known that in rare cases, if used at high concentrations, interference due to the excipients present may occur [8,9].

Overall, these validation data supported the possibility to use CHORUS Promonitor devices in clinical practice to manage TDM of patients with inflammatory diseases.

The validation process is the same for all commercially available immunoassays; however, some differences between kits have been reported in the literature. Laserna-Mendieta et al. compared Promonitor (Grifols, Barcelona, Spain) and Lisa-Tracker ELISA (Theradiag, Croissy-Beaubourg, France) kits to assess the interchangeability of these methods and evaluate the agreement among them for the currently accepted therapeutic ranges [13]. Data indicated relevant quantitative differences between the two assays, which could be related both to a different quantification range, and to a different affinity of the antibodies to the target molecule, but the high agreement in determining subtherapeutic levels of ADL minimized the impact on clinical decision-making. However, a slight systematic bias was noticed between the two ELISA assays impeding the interchangeability [13].The same research group investigated the ability to measure anti-IFX antibodies of the two immunoassays, highlighting the need for further improvements to achieve reliable antibody detection as the agreement between Promonitor and Lisa Tracker ELISA anti-infliximab kits was 82.5 % [13]. Dilutions of ADL or anti-ADL positive sera were assessed for the recovery rate and precision using the following 4 kits: LISA-Tracker, Promonitor, Ridascreen (R-Biopharm, Darmstadt, Germany), and Shikari (Matriks Biotek, Gölbaşi, Ankara, Turkey) [14]. Also in this study, although all kits performed well and precisely, the inter-kit variability suggested the same method should be used always to compare patients' anti-ADL levels in a determined clinical site [14].

The discrepancies among the available commercial kits and among different quantification methods make it necessary to choose the assay for TDM at the beginning of the treatment and maintained during the disease evolution. In such decision making, in addition to the performance specifications, it could be important to consider other parameters, as the usability and cost savings [7].

CHORUS Promonitor is an automated, user-friendly, and ready-to-use kit, with which the possibility of manual errors is minimized as the operator is only required to dispense the serum sample into a well. Each sample is individually processed, thus overcoming the need of using a 96-well plate with the consequent cost and timesaving, as waiting for a sample batch is not required; CHORUS instrument automatically performs a dual dilution to correctly dose in the entire dilution range, thus saving time and work for operators. Overall, CHORUS test takes approximately 2 h and 30 min from the time the instrument is activated to the time of the report result. The manual method, in addition to taking 2 h and 30 min to perform the test (time strictly related to the incubations of the reagents, excluding all the pre-analytical part), involves substantial effort on the part of the operator to plan/set up the analysis (sample dilution) as well as processing the raw data to obtain the final report. CHORUS TRIO is designed to perform everything from sample dilution to printing the final report. Another advantage of the CHORUS TRIO instrument is the ability to memorize the calibration of each lot without repeating it at every run. Furthermore, the same kit can detect both the originator drug and biosimilars. The use of Promonitor kits to quantify both IFX and ADL biosimilars in several inflammatory diseases is consolidated; the potential use of CHORUS devices in TDM during the treatment with biosimilars is supported by the data presented here.

5. Conclusion

CHORUS Promonitor kits were validated assays to quantify IFX, ADL, and their anti-drug antibodies in clinical practice. During preclinical development, these kits resulted as sensitive, specific, accurate, and able to quantify either the reference drug or the corresponding biosimilars. All these features support their use in clinical practice for therapeutic drug monitoring of patients with inflammatory diseases under treatment with IFX or ADL. The easy-to-use completely automated system, which reduces operator intervention, minimizing the possibility of manual errors and the time spent to process each sample, may represent further drivers of choice in favour of CHORUS Promonitor devices. The automated system is particularly useful when dosing of drug and anti-drug must be performed simultaneously to monitor TDM.

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CRediT authorship contribution statement

Helena Cerutti: Conceptualization, Data curation, Formal analysis, Supervision, Validation, Visualization, Writing – original draft. **Giulia Tesi:** Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. **Francesco Petrini:** Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. **Tommaso Bandini:** Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. **Alessandra Cartocci:** Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. **Andrea Ianniello:** Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. **Alessia Bogi:** Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. **Chiara Muzzi:** Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. **Alessandra Brogi:** Data curation, Formal analysis, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Cerutti H, Tesi G, Petrini F, Bandini T, Ianniello A, Bogi A, Muzzi C, Brogi A declare to be "DIESSE Diagnostica Senese S.p.A. Società Benefit" employees. No other conflict of interest has been reported.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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