Diagnostic Accuracy Study

Medicine

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Performance of Remsima® Monitor Drug Level versus RIDASCREEN IFX Monitoring in therapeutic drug monitoring of infliximab in patients with inflammatory bowel disease

A study of diagnostic accuracy

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Abstract

Therapeutic drug monitoring (TDM) is effective in optimizing the efficacy of infliximab in patients with inflammatory bowel disease (IBD). An affordable way of monitoring is in high demand. This study evaluated the analytical and clinical performances of the newly available Remsima monitor kits and compared them with the established enzyme-linked immunosorbent assay kits. The trough level of infliximab in patients with IBD treated with an infliximab originator (Remicade) or biosimilar compounds (Remsima and Remaloce) was measured using a Remsima® Monitor Drug Level (Remsima) kit at the Samsung Medical Center, Seoul, Korea. Twenty-six plasma samples were collected immediately before the infusion of infliximab from 18 patients with IBD (Remicade, n = 8; Remsima, n = 6; and Remaloce, n = 4). The intra-assay intraclass correlation coefficient (ICC) of the RIDA and Remsima kits was 0.951 (95% CI = 0.908–0.976) and 0.990 (95% CI = 0.981–0.995). The inter-assay ICC of infliximab trough level between the RIDA and Remsima kits was very high (R = 0.971; 95% CI = 0.935–0.987), and the mean difference between the kits was 1.458 (95% limits of agreement = –3.302 to 6.219). The intra- and inter-assay reliabilities of all types of infliximab did not show significant differences. Qualitative stratification revealed substantial similarities between the kits (weighted kappa = 0.798). This study indicated that the Remsima kit was reproducible and highly correlated with the RIDA kit.

Abbreviations: IBD = inflammatory bowel diseases, ICC = intraclass correlation coefficient, LoA = limits of agreement, TDM = therapeutic drug monitoring, TL = trough level, TAXIT = trough level adapted infliximab treatment study, TNF = tumor necrosis factor-α.

Keywords: inflammatory bowel disease, infliximab, therapeutic drug monitoring

1. Introduction

Infliximab, a chimeric anti-tumor necrosis factor-α (TNF) monoclonal antibody, induces clinical and endoscopic remission, improves the quality of life, and lowers the risk of surgery and hospitalization in patients with inflammatory bowel diseases (IBD).[1,2] However, up to one-third of patients with IBD showed a primary nonresponse to infliximab, and up to 50% of the patients discontinued infliximab due to loss of response over time or severe side-effects.[3,4] The pharmacokinetics of infliximab contributes to the development of anti-TNF therapy failures. Numerous observational studies and post hoc analyses of randomized control trials indicate that a higher trough level (TL) of infliximab was associated with favorable short- and long-term outcomes in patients with IBD.[5–9] Therefore, therapeutic drug monitoring (TDM) of infliximab is recommended to optimize infliximab treatment.[10–12]

The Remsima® Monitor Drug Level ELISA kit (Remsima kit) was recently introduced to measure free Remsima® in EDTA plasma and serum.[13] Remsima, an infliximab biosimilar, is highly similar and interchangeable to the originator of infliximab (Remicade) in terms of safety, purity, and potency.[14] Therefore, the Remsima kit also measures the drug

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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concentration of other types of infliximab. The Remsima kit is affordable, which may increase accessibility over existing infliximab ELISA kits. Therefore, our study evaluated the analytical and clinical performances of the Remsima kit when measuring infliximab concentrations, and compared it to the TDM kit used in clinical practice. Though there is no reference standard to measure infliximab levels, several TDM studies, including the landmark randomized controlled trial, trough level adapted infliximab treatment study (TAXIT), uses the RIDASCREEN Monitoring Kit (RIDA kit). Therefore, our study evaluated the reliability of the Remsima kit as compared to that of the RIDA kit. Furthermore, the concordance rate of the therapeutic outcome of both assays was assessed using the cutoff therapeutic infliximab level of 3 to7 μg/mL, based on the TAXIT trial.[15]

2. Methods

2.1. Samples

Twenty-six plasma samples were collected immediately before infusion of infliximab (Remicade, n = 8; Remsima, n = 12; and Remaloce, n = 6) from 18 patients with IBD (16 Crohn disease and 2 ulcerative colitis, Fig. 1 and Table 1) at the Samsung Medical Center, Seoul, Korea, between February and June 2020. Infliximab was administered according to a therapeutic protocol consisting of intravenous administration of infliximab at 5 mg/kg during 2 hour infusions at weeks 0, 2, and 6 (induction phase), followed by a maintenance phase in which infusions were administered every 8 weeks. For patients who lost their initial response, the doses were increased from 5 to 10 mg/kg. A total of 10 mL of whole blood was collected in EDTA tubes immediately before infliximab infusion, and the serum was isolated using centrifugation. The study protocol was approved by the Institutional Review Board of the Samsung Medical Center (2019-05-079-001).

2.2. Enzyme-linked immunosorbent assays

The serum level of infliximab was measured using the Remsima kit (Immundiagnostik AG, Bensheim, Germany) and the RIDA kit (R-Biopharm AG, Darmstadt, Germany) according to the manufacturer's instructions. In the first step, the free infliximab of a sample was bound to the specific monoclonal anti-infliximab antibody coated on the plate, followed by washing to remove the unbound substances. The incubation step utilized a peroxidase-labeled antibody and tetramethylbenzidine was used as a peroxidase substrate. Finally, an acidic stop solution was added to terminate the reaction. The absorbance values of the samples were read at 450 and 405 nm using a SpectraMax ABS Plus microplate reader (Molecular Devices, San Jose, CA). All assays were conducted in triplicate.

Each sample was tested using 1 RIDA kit (technical triplicate) and 2 different Remsima kits (Remsima kit #1, technical triplicate; Remsima kit #2, technical duplicate).

2.3. Statistical analysis

The sample size was estimated as 26 to achieve 80% power and significance level (α) < 0.05 to detect differences of 1 μg/mL between paired samples, assuming a pooled standard deviation of 1.75 μg/mL obtained using the paired *t* test.[16]

Categorical variables are presented as absolute values and percentages and analyzed using the unpaired Student *t* test and the Mann–Whitney *U* test. Infliximab concentrations with repeated measurements using different assays are shown in the scatterplot.

Intra-assay variation for each kit was assessed from the linear correlation coefficient (r) and intraclass correlation coefficient (ICC).[17,18] Inter-assay variation between both kits was analyzed using the *R* value and Bland–Altman analysis. Inter-assay

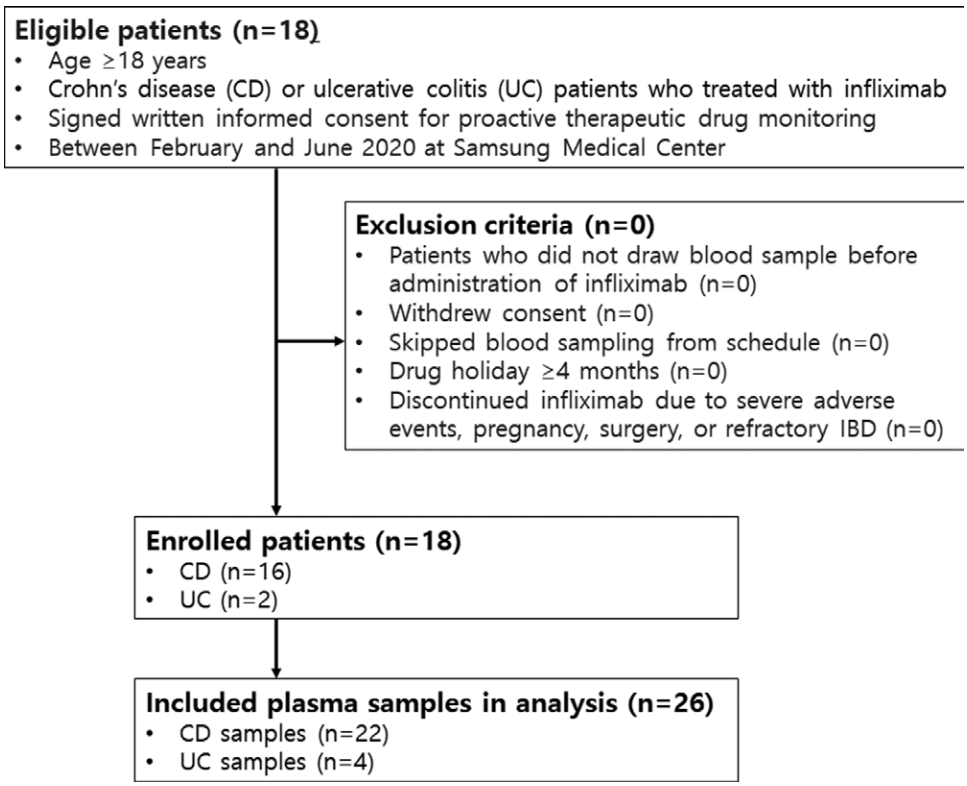

Figure 1. Flow diagram of enrolled patients.

Table 1

Baseline characteristics of the enrolled patients.

		N = 18
Sex	Male	16 (88.9)
	Female	2 (11.1)
Age at diagnosis (yr)	<17	0
	17–40	14 (77.8)
	>40	4 (22.2)
Type of IBD	CD	16 (88.9)
	UC	2 (11.1)
Indications for starting infliximab	Active luminal	17 (94.4)
	Fistulizing	1 (5.6)
Type of infliximab treatment	Induction	6 (33.3)
	Maintenance	12 (66.7)
Type of infliximab agent	Remicade	8 (44.4)
	Remsima	6 (33.3)
	Remaloce	4 (22.2)
Montreal classification		
CD: Location	Ileum	3 (18.8)
	Colonic	0
	Ileocolonic	13 (81.3)
CD: Behavior	Inflammatory	5 (31.3)
	Stricturing	4 (25.0)
	Penetrating	7 (43.8)
CD: Perianal disease	No	6 (37.5)
	Yes	10 (62.5)
CD: Upper GI involvement	No	12 (75.0)
	Yes	4 (25.0)
UC: Disease extent	Proctitis	0
	Left-side	0
	Extensive	2 (100.0)
Concomitant use of immunomodulator	No	5 (27.8)
	Yes	13 (72.2)
Concomitant use of 5-ASA	No	13 (72.2)
	Yes	5 (27.8)

5-ASA = 5-acetylsalicylic acid, CD = Crohn disease, GI = gastrointestinal, IBD = inflammatory bowel disease, UC = ulcerative colitis.

reproducibility was evaluated according to the type of infliximab: Remicade (Janssen Pharmaceuticals, Beerse, Belgium), Remsima (Celltrion, Incheon, Korea), and Remaloce (Samsung Bioepis, Incheon, Korea).

The concordance of both assays was estimated by calculating the overall percentage of agreement, and the weighted kappa statistics were determined after stratification of infliximab concentration by therapeutic interval (<3, ≥3 to <7, and ≥7 μg/mL).[19] A P value <.05, used to determine statistical significance. All statistical analyses were conducted using GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA) and RStudio (Version 1.4.1717) with the IRR package (Version 0.84.1).

3. Results

3.1. Intra-assay variation

The intra-assay variation for all paired repeated measurements using the same assay was excellent, with correlation coefficients ranging between 0.943 and 0.999. Each TL of infliximab with repeated measurements using the RIDA and Remsima kits is illustrated as scatterplots (Fig. 2). The ICCs of the RIDA kit and Remsima kit were 0.951 [95% confidence interval (CI), 0.908–0.976] and 0.990 (95% CI, 0.981–0.995), respectively, suggesting a very strong agreement between the kits.

3.2. Repeatability of Remsima monitor kits

There was a high correlation between infliximab TL measured using the different Remsima kits (Remsima kits #1 and #2, R = 0.924, 95% CI = 0.836–0.966; Fig. 3A). Using the Bland–Altman method, the mean difference between Remsima kit #1 and #2 was –2.379, and the 95% limits of agreement (LoA) ranged from –12.280 to 7.527. The repeatability of the Remsima monitoring kit showed acceptable agreement (Fig. 3B).

3.3. Inter-assay variation of RIDA and Remsima kit

The variation between assays was assessed using the TL measured by the RIDA kit and Remsima kits #1 and #2. There was a high inter-assay correlation between the TLs of infliximab measured by the RIDA and Remsima kits (R = 0. 971, 95% CI = 0.935–0.987). The TLs of infliximab measured using the RIDA and Remsima kits are illustrated using scatterplots (Fig. 4A). The mean difference between the two measurement methods was 1.458, and the 95% LoA ranged from –3.302 to 6.219, suggesting an acceptable agreement (Fig. 4B). This difference appeared to increase with an increase in the TL of infliximab.

3.4. Inter-assay reproducibility according to the type of infliximab

The median level of infliximab trough was 6.97 (1.35–18.84) with the Remsima kit and 8.8 (2.55–18.93) with the RIDA kit (P = .608). The Remsima kit was designed as a TDM tool that measured the drug concentration remaining in the plasma and was evaluated in patients treated with Remsima. Therefore, the reproducibility of the inter-assay was assessed based on the type of infliximab.

The eight samples from patients administered with Remicade, the infliximab originator, showed a high correlation between the Remicade TLs measured by the RIDA and Remsima kits

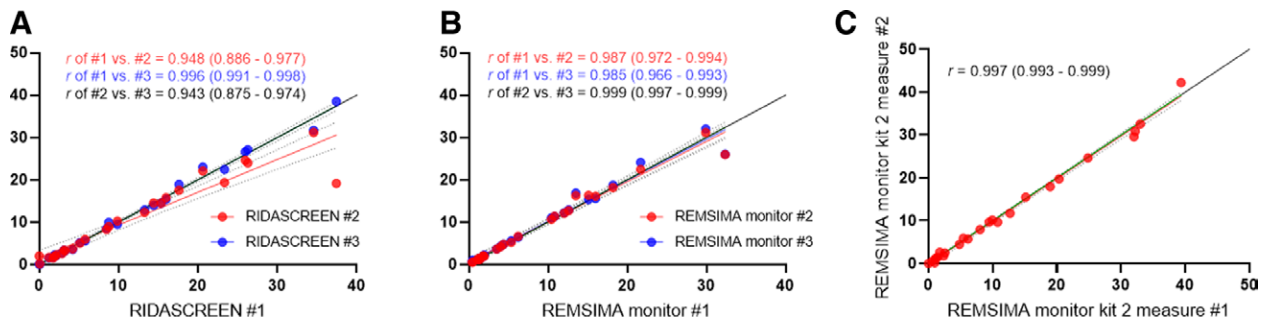

Figure 2. Scatterplots for each infliximab trough level with repeated measurement using (A) RIDASCREEN Monitoring Kit and (B and C) Remsima Monitor Drug Level. r = correlation coefficient.

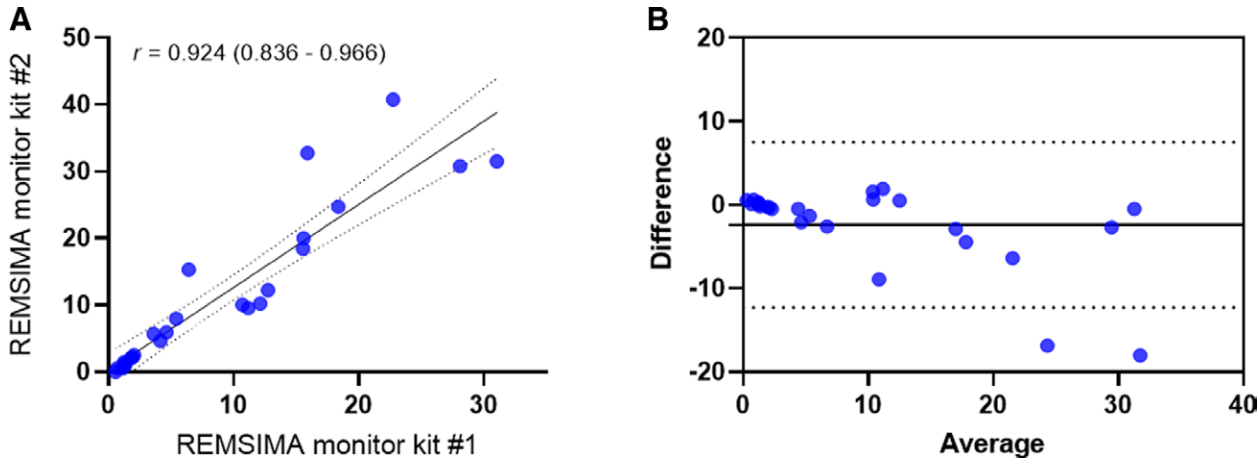

Figure 3. Repeatability of Remsima Monitor Drug Level. (A) Correlation between the trough levels of infliximab from the Remsima kits #1 and #2, represented as a scatter plot. (B) Mean difference between the Remsima kits #1 and #2 in the Bland–Altman analysis. The bias and 95% limits of agreement are represented by horizontal dotted lines. r, correlation coefficients.

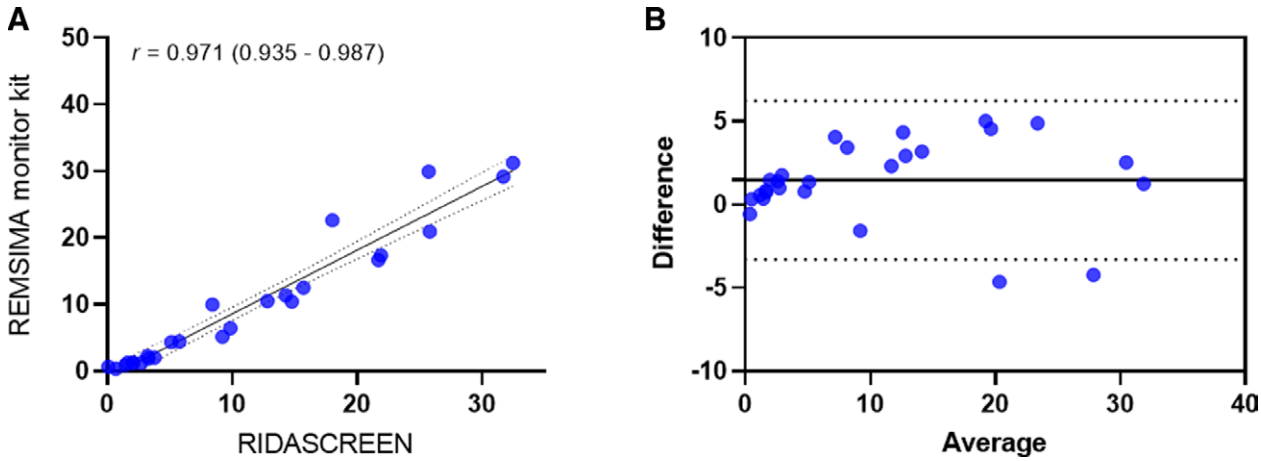

Figure 4. Inter-assay variation of the RIDASCREEN Monitoring Kit and Remsima Monitor Drug Level. (A) Correlation of the tough level of infliximab between kits in scatter plot and (B) mean difference between kits in Bland–Altman analysis. The bias and 95% limits of agreement are represented by horizontal dotted lines. r, correlation coefficients.

(*R* = 0.988, 95% CI = 0.931–0.998; Fig. 5A). The mean difference between the kits was 1.464 (95% LoA = –1.627 to 4.554; Fig. 5B).

In the cases of 12 samples treated with Remsima, biosimilar infliximab, the correlation of Remicade TL measured by from both the kits was very high (*R* = 0.956, 95% CI 0.846–0.988; Fig. 5C) and the mean difference between the kits was 1.391 (95% LoA = –3.694 to 6.475; Fig. 5D).

For the 12 samples from patients treated with Remaloce, the other biosimilar infliximab, there was a high correlation between the Remaloce TL measurements from both the kits (*R* = 0.967, 95% CI = 0.725–0.997; Fig. 5E) and the mean difference between the kits was 1.587 (95% LoA = –4.966 to 8.139 75; Fig. 5F).

3.5. Classification of infliximab TL measured by RIDA and Remsima kits

The concordance of the therapeutic outcome based on the TL of infliximab measured by the two assays was evaluated. Qualitative stratification was conducted depending on the therapeutic intervals suggested in the TAXIT trial (3–7 μg/mL).[15] Substantial agreement was observed between the RIDA and Remsima kits, with a weighted kappa of 0.798 (Table 2). However, we observed that the RIDA kit gave a higher TL category than the Remsima kit, leading to a classification discrepancy in 5 out of 26 samples (19.2%).

4. Discussion

This study reveals the analytical and clinical performances of the newly available Remsima kit for infliximab TDM, and compares the same with the established infliximab RIDA ELISA kit. The ICCs of the RIDA and Remsima kits were 0.951 (95% CI = 0.908–0.976) and 0.990 (95% CI = 0.981–0.995), respectively. The repeatability of the Remsima kit showed acceptable agreement (–2.379, 95% LoA –12.280 to 7.527). There was a high inter-assay correlation of infliximab TL between the kits (*R* = 0.971, 95% CI = 0.935–0.987), and the mean difference between the kits was 1.458 (95% LoA –3.302 to 6.219), suggesting an acceptable agreement. The inter-assay reproducibility according to the type of infliximab was also high. Qualitative stratification based on the therapeutic intervals in the TAXIT trial (3–7 μg/mL) indicated substantial agreement between both assays (weighted kappa = 0.798).

Many commercial assays are available for measuring the TL of infliximab, and the experimental results were

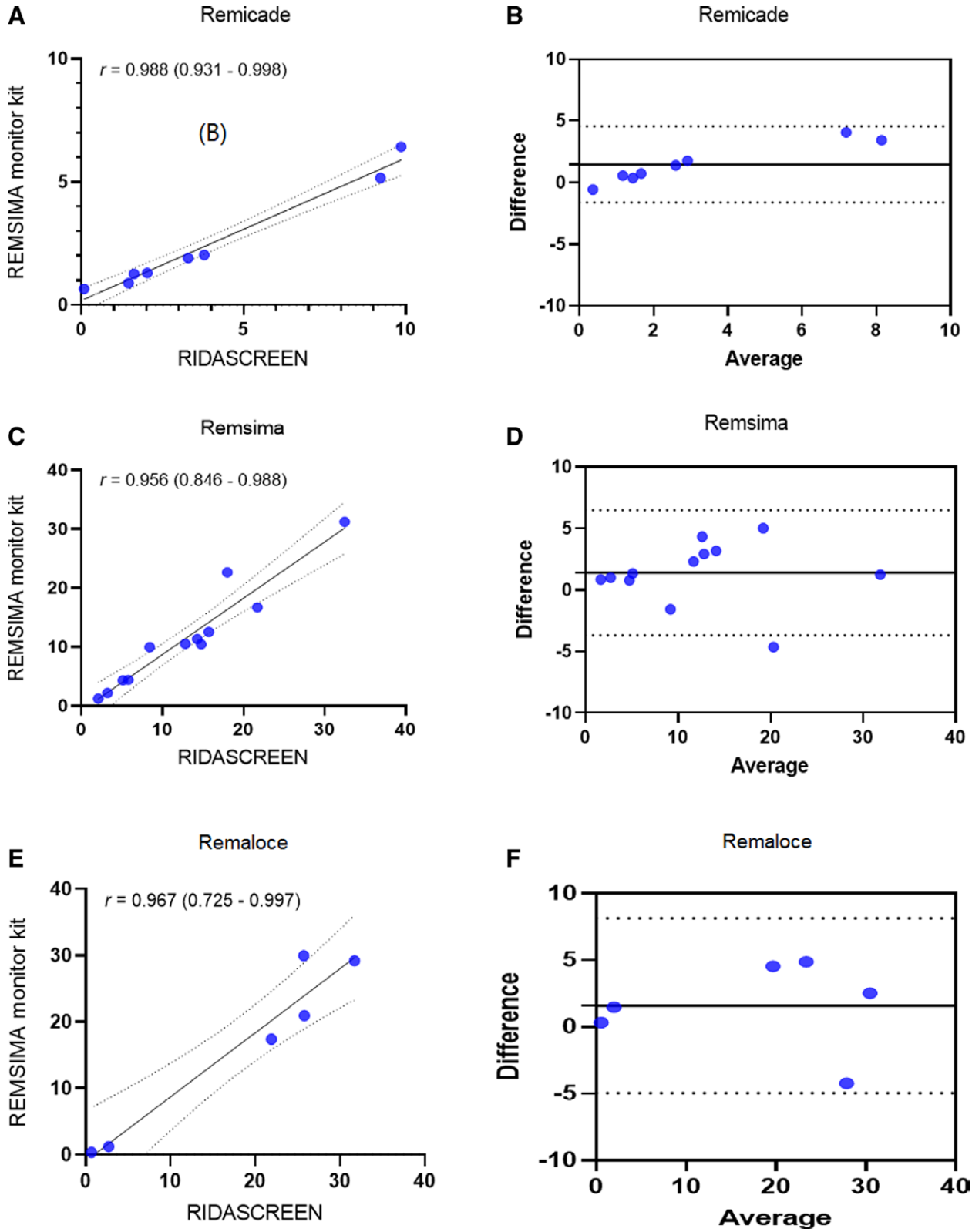

Figure 5. Inter-assay reproducibility of the RIDASCREEN Monitoring Kit and Remsima Monitor Drug Level, according to the type of infliximab. Correlation of the trough level of (A) Remicade, (C) Remsima, and (E) Remaloce between kits, represented as a scatterplot. Mean difference between (B) Remicade, (D) Remsima, and (F) Remaloce kits as per the Bland–Altman analysis. The bias and 95% limits of agreement are represented by horizontal dotted lines. *r* = correlation coefficients.

Table 2

Classification of infliximab trough concentration measured by RIDASCEERN and REMSIMA kit.

	RIDASCREEN kit			
	<3 μg/mL	3–7 μg/mL	≥7 μg/mL	Weighted Kappa statistics
REMSIMA monitor kit				
<3 μg/mL	7	3	0	Kappa = 0.798
3–7 μg/mL	0	2	2	
≥7 μg/mL	0	0	12	

comparable with acceptable accuracy and reproducibility between assays.[20–24] Most studies reported average coefficient of variations on comparing the accuracy and reproducibility between brand-new assay kits and the widely used assay kits, including the RIDA kit. However, our study additionally analyzed the ICC, Bland–Altman, and weighted Kappa values.[20,21] Based on these analyses, the Remsima kit was found to be reproducible and highly correlated with the RIDA kit. A study using infliximab and two biosimilars demonstrated reproducibility not only between infliximab and the biosimilars, but also between biosimilars, consistent with our results (infliximab originator vs. biosimilars: 0.947–0.978 vs 0.971).[23]

TDM plays a key role in ensuring the optimization of anti-TNF therapy, but there are barriers to applying TDM in clinical practice.[25,26] The existing TDM methods are expensive when used routinely and proactively in practice. However, from a long-term perspective, proactive TDM may result in lower costs and fewer adverse side-effects through effective individualized treatment.[15,27] Therefore, competitively priced TDM kits must be made available. After the generalization of TDM clinically, proactive TDM could be applied in practice, which could lead to improved clinical outcomes in patients with IBD.

Although a higher TL of infliximab was associated with better outcomes in patients with IBD, there was no defined gold standard assay for the quantification of infliximab TL. Moreover, the cutoff value of TL might differ depending on the therapeutic goals. Studies examining the impact of infliximab TL in IBD have shown various clinical endpoints, from clinical remission to histological remission, and differences in cutoff values using different TDM assays. The target TL of infliximab has been recommended to be 3 to 7 μg/mL, based on the TAXIT trial. However, variability among TDM kits might influence clinical outcomes accompanied with treatment decisions, depending on the cutoff value of infliximab TL. In this study, we demonstrated qualitative stratification depending on the therapeutic intervals suggested in the TAXIT trial, with acceptable agreement.

Our study had some limitations. First, the sample size of our study appeared to be relatively small to represent heterogeneous clinical conditions, even though our sample size showed statistical power. Second, we did not compare the Remsima kit with kits other than the RIDA kit. However, previous studies have shown comparability among the assays. Our study is the first to verify the analytical and clinical performance of the Remsima kit using various statistical methods.

5. Conclusions

This study verified the performance of the Remsima kit compared to the RIDA kit to measure infliximab concentration, regardless of the type of infliximab. The increasing need for proactive TDM and reliable and affordable assays such as the Remsima kit might help in the proactive application of TDM in clinical practice.

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Author contributions

All authors have read and agreed to the published version of the manuscript.

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