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Original Article

Population Pharmacokinetic Model for the Use of Intravenous or Subcutaneous Infliximab in Patients with Inflammatory Bowel Disease: Real-World Data from a Prospective Cohort Study

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Background/Aims: Infliximab treatment failure in patients with inflammatory bowel disease may result from sub-optimal infliximab trough level. An understanding of pharmacokinetics (PKs) is important to maintain an optimal trough level. PK studies of the switch to subcutaneous (SC) infliximab from intravenous (IV) infliximab using real-world data are lacking. We aimed to develop a population PK model of IV and SC infliximab to predict individual infliximab exposure during maintenance therapy.

Methods: We used data from prospectively collected data on IV and SC infliximab concentrations in patients with inflammatory bowel disease receiving maintenance treatment from February 2020 to December 2022 at Samsung Medical Center. Population PK analysis was conducted by using a two-compartment model with first-order absorption and first-order elimination. Goodness-of-fit plots and visual predictive check were used to evaluate the PK model.

Results: A total of 2,132 samples from 181 patients (149 Crohn's disease and 32 ulcerative colitis) were analyzed. We developed an infliximab population PK model using body mass index, albumin, C-reactive protein level, and the anti-drug antibody level and validated its predictive performance.

Conclusions: It may be possible to predict the infliximab trough level of both IV and SC infliximab in patients with inflammatory bowel disease during maintenance treatment by using our model in real-world practice. **(Gut Liver, 2025;19:376-387)**

Key Words: Infliximab; Pharmacokinetic model; Intravenous; Subcutaneous; Inflammatory bowel diseases

INTRODUCTION

Infliximab, an anti-tumor necrosis factor-α agent, is effective for induction and maintenance of remission in patients with inflammatory bowel disease (IBD).[1,2] Many studies have shown that a higher trough level (TL) of infliximab was associated with better short- and long-term outcomes in patients with IBD.[3-7] Therefore, therapeutic drug monitoring (TDM) has been performed for dose optimization.[8,9] Based on Trough Concentration Adapted Infliximab Treatment trial, infliximab TL was recommended to 3–7 μg/mL.[10] Treatment failure might result from sub-optimal infliximab TL, associated with increased clearance (CL). Many factors accounted for the variability observed in infliximab CL, including formation of antibodies to the infliximab, serum albumin (ALB) level, concomitant use of immunomodulator, high degree of inflammation, and sex.[6,9-14] To maintain optimal TL, a thorough understanding of pharmacokinetics (PK) of infliximab is necessary.

Intravenous (IV) administration of infliximab results in an early and rapid peak concentration, followed by a steady decline to TLs.[15-18] Among the various types of IV

infliximab, Remsima stands out as the first infliximab biosimilar, highly resembling and interchangeable with the originator of infliximab (Remicade) in terms of safety, purity, and potency.[19,20] The recently introduced subcutaneous (SC) infliximab, Remsima SC, has demonstrated noninferiority to IV infliximab in a randomized, open-label study.[21] Across the published data, SC infliximab has shown relative PK stability and higher TLs compared to IV infliximab.[22] Recent studies have shown that switching to SC infliximab resulted in durability and effectiveness with similar safety profiles in IBD patients with maintenance therapy.[23-27]

Population PK models allowed for optimizing drug dosing by quantifying the covariates contributing to drug levels.[28] Although numerous population PK studies have been conducted on IV infliximab, few have investigated SC infliximab.[21,29] However, in those studies, dense sampling was performed by dividing the IV and SC-administered groups, whereas in clinical settings, only trough concentrations were sampled. Therefore, there is a need for studies based on sparsely sampled data from real-world settings. Additionally, using TDM data allows for obtaining both IV and SC drug concentrations in the same patient. Therefore, our study aimed to develop population PK model of IV and SC infliximab that accurately predicts individual infliximab exposure during maintenance therapy using prospectively collected data in terms of TDM.

MATERIALS AND METHODS

1. Study design and patients

This study was a population PK model in IBD using prospectively collected IV and SC infliximab concentrations from February 2020 to December 2022 at Samsung Medical Center, Seoul, Korea. The inclusion criteria were as follows: (1) patients with Crohn's disease (CD) or ulcerative colitis (UC); (2) those who were treated with maintenance IV infliximab; and (3) those who agreed with informed consent for proactive TDM with measurements of TL of pre-dose infliximab concentration and titer of anti-drug antibody (ADA; neutralizing antibodies related to immunogenicity). Exclusion criteria were as follows: (1) withdrew consent; (2) drug holiday ≥4 months; and (3) patients who were immediately switched to maintenance therapy with SC, after induction therapy with IV infliximab.

The Institutional Review Board of Samsung Medical Center approved the conduct of this study (IRB number: 2019-05-079). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in prior approval by the institution's human research committee. Written informed consent was obtained.

2. Infliximab maintenance therapy with dose optimization based on TDM

The enrolled patients received induction therapy with 5 mg/kg IV infliximab (Remicade, Janssen Pharmaceutica, Beerse, Belgium; Remsima, Celltrion, Incheon, Korea; and Remaloce, Samsung Bioepis, Incheon, Korea) at 0, 2, and 6 weeks; and were administered 5 mg/kg IV, as maintenance, every 8 weeks.[30,31]

The dosage of infliximab was adjusted based on the TL of infliximab. Patients with sub-therapeutic TLs (<3 μg/mL) were considered for dose escalation of infliximab to 10 mg/kg, switching to SC infliximab, or transitioning to another biologic agent. SC infliximab (Remsima SC, Celltrion) was administered via a single SC injection with a prefilled pen containing 120 mg infliximab every 2 weeks. In patients with UC, Korean insurance did not permit dose escalation to 10 mg/kg. These patients were considered for switching to SC infliximab or another biologic agent. Patients who were already receiving 10 mg/kg of IV infliximab were considered for switching to SC infliximab or another biologic agent if they had sub-therapeutic TL. On the other hand, the patients with therapeutic TL (≥3 μg/mL) of infliximab were administrated the same dose of infliximab administrated previous infusion.

3. IV and SC infliximab therapy during follow-up

During the study period, regardless of TL, patients who experienced a loss of response during maintenance therapy with 5 mg/kg IV infliximab were either escalated to 10 mg/kg every 8 weeks, switched to SC infliximab, or transitioned to another biologic agent.[32,33] For patients receiving an escalated dose of infliximab, switching to SC infliximab or transitioning to other biologics was considered. In patients with UC, Korean insurance did not permit dose escalation to 10 mg/kg. These patients were considered for switching to SC infliximab or transitioning to another biologic agent. For patients treated with SC infliximab, a change to other biologics was recommended.

4. Data collection and processing

Demographic information, including age, sex, body weight (BW), height, body mass index (BMI), and the laboratory findings, including white blood cell count, ALB, and C-reactive protein (CRP) levels and PK profile, including serum TL levels of infliximab and ADA, were collected at every outpatient clinic visiting. Also, clinical characteristics of patients were collected from enrollment, prospectively. The clinical features were as follows: age at the diagnosis,

Montreal location (L1, ileum; L2, colon; or L3, ileocolon), behavior (B1, no strictures and no penetration; B2, strictures; or B3, penetration) and perianal modifier (with or without perianal disease) in CD and Montreal disease extent in UC (E1, ulcerative proctitis; E2, left-sided UC; and E3, extensive UC), history of smoking and intestinal operation, indication for infliximab (luminal or fistulizing CD), type of infliximab, and use of concomitant immunomodulator. Also, remnant disease burden of patients at the enrollment assessed. In CD, transmural healing was defined as global simplified magnetic resonance index of activity (sMaRIA) of 0. The sMaRIA was calculated using the following formula: [1×wall thickness (>3 mm)] + [1×mural oedema (hyperintense signal on fat-saturated T2-weighted images)] + [1×fat stranding (increased T2-weighted signal intensity in mesenteric fat adjacent to bowel loops due to oedema/fluid in perienteric fat)] + [2×ulcers].[34] The global sMaRIA score was calculated as summation of the sMaRIA scores in the rectum, sigmoid colon, descending colon, transverse colon, ascending colon and ileum.[35] In case of no magnetic resonance enterography imaging, we assessed complete endoscopic remission, defined as the Simple Endoscopic Score for Crohn's Disease (SES-CD) of 0.[36] The International Organization for the Study of Inflammatory Bowel Diseases has defined endoscopic remission in CD as a SES-CD of 0–2. However, in our study, we assessed SES-CD in 43 CD patients who did not undergo magnetic resonance enterography and could not be evaluated transmural healing. We strictly defined SES-CD score of 0 as complete endoscopic remission, considering equity in 106 CD patients who underwent magnetic resonance enterography and were assessed transmural healing. SES-CD was assessed during colonoscopy or single-balloon enteroscopy by the endoscopist based on the size of mucosal ulcers, ulcerated surface, endoscopic extension and the presence of stenosis in the ileum, right colon, transverse colon, left colon and rectum regardless of previous bowel resection.[37] In UC, endoscopic remission was defined as a Mayo endoscopic score of 0.

5. Collection and processing of PK data

A total of 10 mL of whole blood was collected in ethylenediaminetetraacetic acid tubes immediately before infliximab infusion, and the serum was isolated using centrifugation. The serum level of infliximab was measured using the Remsima kit (Immundiagnostik AG, Bensheim, Germany) according to the manufacturer's instructions.[38,39] Free infliximab was quantitatively measured via enzyme immunoassay. The serum was diluted with dilution buffer at a ratio of 1:200. During the incubation step, free infliximab binds to antibodies coated on the plate. After removing unbound substances, peroxidase-labeled antibody, tetramethylbenzidine, and acidic stop solution were sequentially applied. The intensity of the yellow color, which is proportional to the concentration of free infliximab, was measured with an enzyme-linked immunosorbent assay reader.

Additionally, the free and bound antibodies for infliximab, also known as total ADA, were measured using drug tolerant method. Conventional laboratory techniques, drug sensitive method led to a false negative result, because it could not detect ADA bound to the drug. One way to overcome the problem of drug interference is to use a drug tolerant, precipitation, and acid dissociation assay.[40] Regardless of the amount of drug in the serum, this process allowed for the detection of both free and bound ADA in samples. The ADA above the cutoff value of 10 ng/mL was defined as ADA positive.

During IV administration, concentrations measured at 8±2 weeks after the last dose were utilized for population PK modeling. For SC administration, concentrations measured at 14±4 days after the last dose were utilized for population PK modeling. When the infliximab concentration was below the limit of quantitation of 3 ng/mL, a value of 1.5 ng/mL, which is half of the limit, was used.

6. Population PK modeling

Population PK analysis was conducted using the NONMEM program (ICON Development Solutions, Ellicott City, MD, USA), employing the first-order conditional estimation with interaction method for estimation. The base model was evaluated for both 1- and 2-compartment models with first-order absorption and first-order elimination. Both IV and SC data were used simultaneously in estimating CL, central volume of distribution (Vc), peripheral volume of distribution (Vp), intercompartmental clearance (Q), bioavailability (F), and absorption rate constant (ka). In contrast to previous studies, only sparsely measured concentrations were utilized, necessitating the fixation of Vp and Q to literature-based values (1.96 L and 0.599 L/day, respectively).[29] Additionally, a sensitivity analysis was conducted by adjusting the Vp and Q values based on the 95% confidence intervals reported in the literature, with the confidence interval for Vp ranging from 1.71 to 2.13 and for Q ranging from 74.0 to 84.3.[29] The inter-individual variability was modeled using exponential error model. Inter-individual variability was evaluated for all PK parameters, but it was only included for CL and F. The residual variability was modeled using combined proportional and additive error model.

The covariate model was built using stepwise covariate selection. The criteria for covariate selection were based

on changes in the objective function value of 3.84 ($p<0.05$) for forward selection and changes in the objective function value of 6.63 ($p<0.01$) for backward elimination. Continuous covariates were normalized to the mean value of the data, while both continuous and discrete covariates were incorporated into the base model using power functions. Covariates evaluated for CL included age, sex, BW, height, BMI, diagnosis (CD or UC), ADA, ALB, CRP, and white blood cell. Covariates evaluated for F included BW, BMI, and ADA. ADA was evaluated using both the absolute value and the dichotomized value based on the cutoff of 10 ng/mL.

The adequacy of the PK model fit to the data was assessed through goodness-of-fit plots. Bootstrap with 500 samples and visual predictive check stratified for the route of administration were employed to assess the robustness of the final model. Statistical significance was set at $p<0.05$. All statistical analyses were performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Characteristics of the study population

A total of 212 IBD patients were eligible for this study. Thirty-one patients were excluded for the following reasons: withdrew consent (n=1), drug holiday >4 months (n=5), or immediate switch to SC maintenance after IV induction (n=25). Finally, a total of 2,132 samples from 181 patients (149 CD and 32 UC) were used for population PK modeling (Fig. 1). The characteristics of the patients and corresponding measurements for these individuals are presented in Table 1.

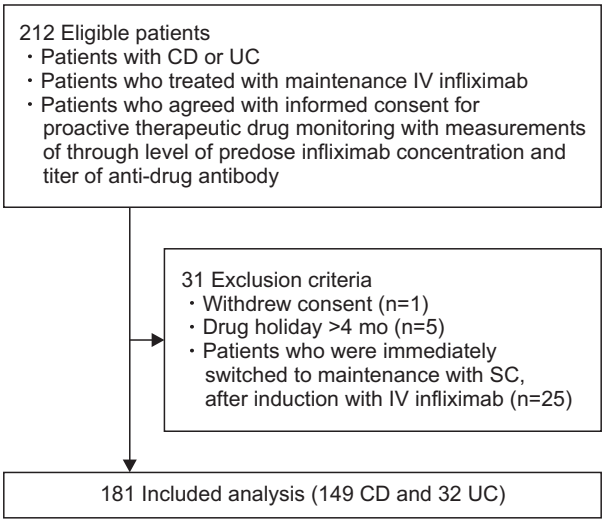

Fig. 1. Flow of study. CD, Crohn's disease; UC, ulcerative colitis; IV, intravenous; SC, subcutaneous.

Table 1. Characteristics of Enrolled Patients for Population Pharmacokinetic Modeling

Characteristics	Value
Demographics	181
Age, median (IQR), yr	36 (30–47)
Male sex	130 (71.8)
Body weight, median (IQR), kg	65.0 (55.0–73.6)
Height, median (IQR), cm	170.0 (162.8–174.2)
Diagnosis	
CD	149 (82.3)
UC	32 (17.7)
Current smoker	25 (13.8)
Previous intestinal surgery	53 (29.3)
Age at diagnosis	
<16 yr	14 (7.7)
17–40 yr	143 (79.0)
>40 yr	24 (68.5)
Montreal classification	
CD: location	
Ileal	39 (26.2)
Colonic	15 (10.1)
Ileocolonic	95 (63.8)
Upper GI	13 (8.7)
CD: behavior	
Inflammatory	60 (40.3)
Stricturing	41 (27.5)
Penetrating	48 (32.2)
CD: perianal disease	82 (55.0)
UC: disease extent	
Proctitis	2 (6.3)
Left side	12 (37.5)
Extensive	18 (56.3)
Remnant disease burden at the enrollment	
CD	
Transmural healing (global sMaRIA score=0)	16/106 (15.1)
Complete endoscopic remission (SES-CD=0)	8/43 (18.6)
UC	
Endoscopic remission (MES=0)	16/32 (50)
Type of infliximab*	
Remicade	112 (61.9)
Remsima	58 (32.0)
Remaloce	11 (6.1)
Indications for infliximab	
Fistulizing	19 (10.5)
Active luminal	162 (89.5)
Concomitant immunomodulator	95 (52.5)
Dose intensification (10 mg/kg) at enrollment	42 (23.2)
Measurements, median (IQR) (n=2,132)	
White blood cell, $\times 10^9$/L	5.7 (4.7–6.8)
Albumin, g/dL	4.4 (4.2–4.6)
C-reactive protein, mg/dL	0.06 (0.06–0.15)
Infliximab trough level, μg/mL	4.6 (2.7–7.3)
ADA concentration, ng/mL	9.3 (7.6–11.6)
ADA positive†	12.6 (11.0–19.0)
ADA negative‡	8.0 (7.1–9.0)

Data are presented as number (%) unless otherwise indicated.
IQR, interquartile range; CD, Crohn's disease; UC, ulcerative colitis; GI, gastrointestinal; sMaRIA, simplified magnetic resonance index of activity; SES-CD, Simple Endoscopic Score for Crohn's Disease; MES, Mayo endoscopic score; ADA, anti-drug antibody.
*At the time of enrollment; †861 measurements; ‡1,271 measurements.

The median age of enrolled patients was 36 years (interquartile range [IQR], 30 to 47 years). Seventy-two percent of patients were male. Transmural healing or complete endoscopic remission was observed in 16.1% of CD patients, while 50% of UC patients showed endoscopic remission at enrollment. Over half of the patients used concomitant immunomodulator. About 30% of patients had previous intestinal surgery. Most patients (61.9%) were treated with Remicade at the time of enrollment. Forty-two patients (23.2%) were already treated with 10 mg/kg IV infliximab at the time of enrollment, while 139 patients (76.8%) were using 5 mg/kg IV infliximab.

The median infliximab TL was 4.6 μg/mL (IQR, 2.7 to 7.3 μg/mL) and ADA was 9.3 ng/mL (IQR, 7.6 to 11.6 ng/mL) in both IV and SC formula. The median infliximab TL was 4.15 μg/mL (IQR, 2.49 to 6.32 μg/mL) in IV formula and 18.65 μg/mL (IQR, 11.70 to 25.06 μg/mL) in SC formula. In 171 patients, ADA tested positive at least once, accounting for 861 out of the total 2,132 measurements. The median ADA value was 12.6 ng/mL (IQR, 11.0 to 19.0 ng/mL) for ADA-positive cases, and 8.0 ng/mL (IQR, 7.1 to 9.0 ng/mL) for ADA-negative cases.

2. Maintenance of infliximab, switch to SC infliximab or change other biologics during follow-up

During follow-up period, 63 of the 139 patients (45.3%) maintained the dose of 5 mg/kg IV infliximab without switching to other biologics including SC infliximab. Forty-five patients (32.4%, 45/139) were escalated the dose of IV infliximab to 10 mg/kg, and 13 patients among them then switched to SC infliximab. One of 13 patients finally changed to other biologics. And two of 45 patients, changed to other biologics without switching SC infliximab. Five patients were changed to other biologics without dose escalation and switching to SC infliximab. Forty-two patients were already treated with 10 mg/kg IV infliximab at the time of enrollment. Among them, 13 patients (31.0%, 13/42) changed to SC infliximab and 5 patients (11.9%, 5/42) changed to other biologics, other than SC infliximab.

3. Development of population PK model

The base model provided the best fit for the two-compartment model with first-order absorption and first-order elimination. The changes in objective function value resulting from the inclusion of covariates during the stepwise covariate selection process were presented in Supplementary Table 1. The final model included ALB, CRP, ADA, and BMI as covariates for CL, and ADA and BMI as covariates for F, as shown in Table 2 along with the estimated values.

In the final model, Vc and ka were estimated to be 1.87 L and 0.083 day^{-1} respectively. CL and F were defined as follows:

$$CL=0.248\times(ALB/4.4)^{-0.372}\times(CRP/0.18)^{0.022}\times(ADA/10)^{0.022}\times(BMI/22.5)^{0.36}$$

$$F=0.667\times(ADA/10)^{-0.213}\times(BMI/22.5)^{-0.832}$$

The values of CRP, ADA, and BMI were positively associated with CL, while ALB was inversely associated with CL. Higher levels of ADA and BMI were associated with lower F. ADA positivity was associated with higher CL (0.261 L/day vs 0.246 L/day) and lower F (0.610 vs 0.762) compared to ADA negativity.

The steady-state trough concentrations during IV and SC administration can be calculated using the following equations derived from the estimated parameters:

TL (at steady state during IV administration) = $\frac{Dose}{Vc}\times\frac{e^{-kel\times\tau}}{1-e^{-kel\times\tau}}$

TL (at steady state during SC administration) = $\frac{F\times Dose}{Vc}\times\frac{ka}{ka-kel}\times\frac{e^{-kel\times\tau}-e^{-ka\times\tau}}{1-e^{-kel\times\tau}}$

Here, kel is the elimination rate constant, calculated as the ratio of CL to Vc. τ is the dosing interval, representing the time between consecutive drug administrations in repeated dosing regimens.

Table 2. Final Estimates and Bootstrap Results

Parameter	Estimates (RSE %)	Bootstrap results, median (95% CI)
CL (L/day)	0.248 (20)	0.249 (0.173 to 0.344)
Vc (L)	1.87 (61)	1.88 (0.23 to 4.36)
Vp (L)	1.96 fixed	-
Q (L/day)	0.599 fixed	-
F	0.667 (19)	0.677 (0.477 to 0.921)
ka (day^{-1})	0.083 (26)	0.083 (0.051 to 0.151)
θ_{ALB-CL}	−0.372 (30)	−0.383 (−0.592 to −0.154)
θ_{CRP-CL}	0.022 (33)	0.023 (0.010 to 0.036)
θ_{ADA-CL}	0.022 (42)	0.021 (0.001 to 0.042)
θ_{BMI-CL}	0.360 (31)	0.354 (0.150 to 0.627)
θ_{ADA-F}	−0.213 (19)	−0.209 (−0.298 to −0.057)
θ_{BMI-F}	−0.832 (33)	−0.838 (−1.450 to −0.300)
ω_{CL} (CV%)	20.3 (8)	20.0 (17.2 to 23.4)
ω_{F} (CV%)	21.6 (19)	21.0 (10.8 to 29.3)
Cov_{CL-F}	0.017	0.017 (−0.002 to 0.039)
Proportional error (σ)	0.333 (6)	0.328 (0.290 to 0.368)
Additive error (mg/L)	0.561 (12)	0.571 (0.438 to 0.732)

RSE, relative standard error; CI, confidence interval; CL, clearance; Vc, central volume of distribution; Vp, peripheral volume of distribution; Q, intercompartmental clearance; F, bioavailability; ka, absorption rate constant; ALB, albumin; CRP, C-reactive protein; ADA, anti-drug antibody; BMI, body mass index; CV, coefficient of variation; Cov, covariance.

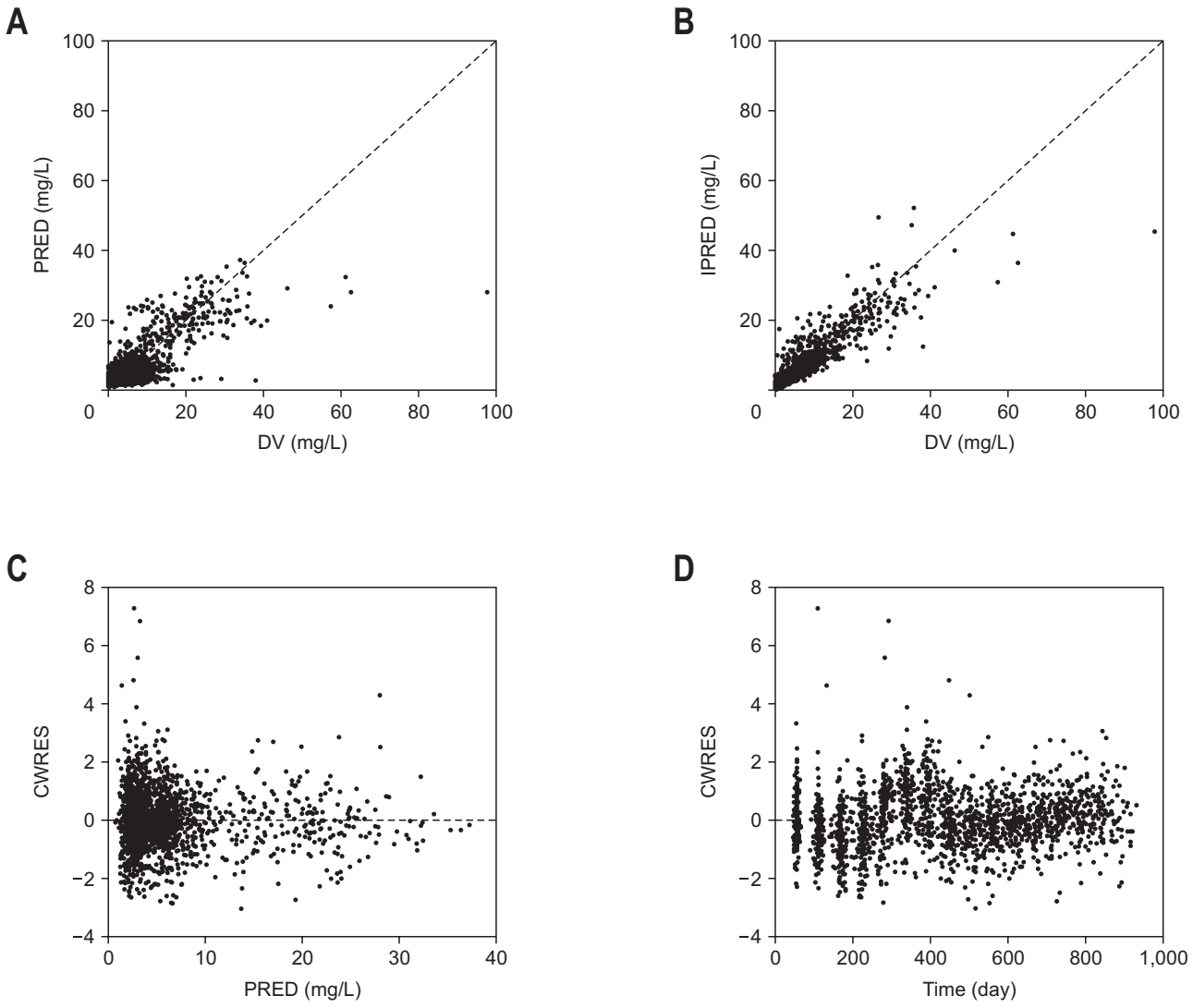

Fig. 2. Goodness-of-fit plots. (A) Observed value (DV) versus population predicted value (PRED), (B) DV versus individual predicted value (IPRED), (C) PRED versus conditional weighted residuals (CWRES), (D) time versus CWRES.

4. Evaluation of PK model

Goodness-of-fit plots were shown in Fig. 2. The observed values closely matched the individual predicted values, with the exception of case where the observed value was extremely large at 97.846. The distribution of conditional weighted residuals with respect to population predicted value or time showed no apparent trend, with the majority of values falling between –2 and 2. Table 2 also presents the bootstrap results. All estimated values were similar to the median values obtained from bootstrapping and fell within the 95% confidence interval. Fig. 3 demonstrates the results of the visual predictive check analysis, indicating that the observed concentrations fall within the predicted intervals of the simulated data.

The sensitivity analysis evaluated the changes in parameter estimates based on variations in the fixed values of Vp and Q (Supplementary Table 2). Changes in estimates, except for Vc, were minimal, and the variation in Vc estimates remained within the bootstrap 95% confidence interval.

DISCUSSION

We used real-world data from prospective cohort study to develop population PK model for IV and SC infliximab that predicted infliximab TL during maintenance therapy in patients with IBD. Indeed, TL from our cohort (4.15 μg/mL in IV and 18.65 μg/mL in SC) showed reasonable levels consistent with previous study for cutoff values required for clinical and biochemical remission in IV and SC formula.[8,41] The final model incorporated BMI, ALB, CRP

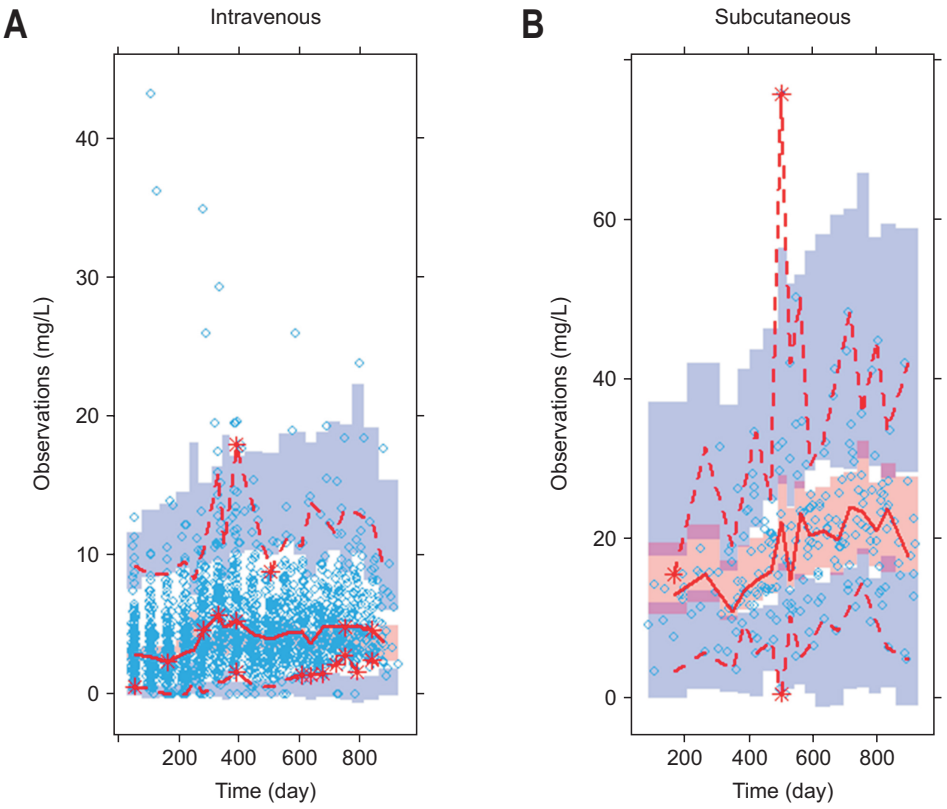

Fig. 3. Visual predictive check plot of final population pharmacokinetic model. (A) Intravenous infliximab and (B) subcutaneous infliximab. The observed concentrations are shown as circles. The solid line and two dashed lines represent the median, 2.5th and 97.5th percentiles of the observations. The red shaded area represents 95% confidential interval (CI) of the simulation median, whereas the blue shaded areas represent 95% CI of the simulation 2.5th and 97.5th percentiles.

and ADA as covariates for CL, with BMI and ADA for F. The diagnosis (CD or UC) not being included as a covariate in the model indicates no significant PK differences between the diseases.

The covariates for CL derived from our study were consistent with those from previous studies. Previous studies showed that CL of IV infliximab increased significantly with low ALB, high BW, and the presence of ADA.[12,29] BW is a common covariate for infliximab, which is administered based on weight-based dosing. However, in patients with obesity or underweight, BMI may better reflect the PK of infliximab. In this study, both BW and BMI were evaluated, and the results demonstrated that BMI provides a superior explanation of infliximab PK. The relationship between serum ALB level and infliximab TL was well-established and ALB was a significant covariate for CL of anti-tumor necrosis factor and other biologics in patients with IBD.[17,29,42-44] ALB binds to many drugs in the body, slowing down their elimination.[45] Additionally, low ALB levels reflected intestinal leakage of severe colitis, which resulted in increased intestinal loss of infliximab.[46] During the course of infliximab treatment, ADA can be developed, enhancing drug CL and neutralizing its effects.[12] The presence of ADA has been used as a covariate for CL in several studies, where its presence has been associated with an increase in CL ranging from 29% to 72%.[12,29,47] However, the distinctive feature of our model was that ADA levels were chosen as covariates rather than the presence of ADA. Actually, there was no absolute cutoff level for ADA, so the presence of ADA might be relatively more ambiguous than ADA level. Furthermore, while binary classification is intuitive, it can lead to information loss. For instance, categorizing ADA levels above 10 ng/mL as positive may overlook the variability within this range. In this study, ADA levels are densely distributed: the median for ADA positive was 12.6 ng/mL, and for ADA negative it was 8.0 ng/mL. Therefore, classifying ADA levels around 10 ng/mL simply as positive and negative can be problematic. Also, our PK model used CRP as another covariate. CRP, which reflected acute systematic inflammation, was widely used to monitor IBD disease activity.[48] Selecting Therapeutic Targets in Inflammatory Bowel Disease, STRIDE II recommends that normalization of CRP is intermediate treatment target in patients with IBD.[49] CRP has been used to evaluate disease severity and predict disease course.[50,51] Moreover, elevated CRP levels were associated with increased CL of infliximab.[52] CRP levels are indicators of intestinal mucosal inflammation, which can lead to increased protein-losing enteropathy and extracellular catabolism of infliximab.[53] To explore potential interactions among covariates, we incorporated interaction terms among covariates included in the final model to evaluate their impact on CL and F. However, the inclusion of these terms did not lead to significant improvement in the model's performance. This suggested

that the effects of the individual covariates on CL and F are additive, rather than interactive.

The incomplete absorption and lower F of SC infliximab compared to IV infliximab can be attributed to the restricted transport of monoclonal antibodies through the hypodermis.[54] The population estimate of F for SC infliximab derived in our study, 0.667, was consistent with previously reported values ranging from 0.576 to 0.791.[21,29] In previous studies, the F of SC infliximab was not found to be affected by BMI.[21,29] However, in our study, BMI was included as a covariate. The thickness of the hypodermis increases with BMI, which has been identified as a negative covariate affecting the F of therapeutic antibodies.[55] In addition, ADA was identified as a covariate affecting F in our study. The absorption of infliximab can be reduced by pre-systemic catabolism via ADA.

During follow-up study period, 64 out of 139 patients (45.3%) who were treated with 5 mg/kg IV infliximab at enrollment, sustained infliximab treatment without change. Considering that the loss of response over time is 50%, it is relevant findings. Five patients changed to other biologics without dose escalation and switched to SC infliximab. Four out of five patients showed that relatively low TL <1 μg/mL with positive ADA. And 86 patients did not use concomitant immunomodulator at the enrollment. Among them, 17 patients (19.8%, 17/86) finally used immunomodulator during follow-up periods. Most of them (15/17) did not need to change other biologics after adding concomitant immunomodulator; however, five patients switched to SC infliximab to sustain optimal TL. The effect of immunomodulators on infliximab CL was presumed to occur through the decreased formation of ADA. However, this relationship has not been universally identified in previous PK models.[12,47] In clinical practice, clinicians tended to prescribe concomitant immunomodulator for patients those who showed low infliximab level or presence of ADA. Therefore, patients already treated with concomitant immunomodulator at the enrollment, were more likely to had lower TL than patients without concomitant immunomodulator. Moreover, more than half of our study patients already used immunomodulators at the enrollment. Even though we did not figure out effect of immunomodulators on infliximab TL, but we found that immunomodulators were clinically useful to maintain the optimal TL without changing treatment.

For practical reasons, TLs were incorporated into TDM algorithms for IV infliximab. However, it was unclear whether TL was the optimal exposure measure to guide clinical decision nor if it had the strongest correlation with therapeutic efficacy.[29,56] Indeed, previous randomized controlled trial showed that clinical indicators were similar, not superior, even though SC infliximab revealed higher TL compared to IV infliximab.[21] In our study, the TLs of infliximab were higher in SC administration than in IV administration (18.65 μg/mL vs 4.15 μg/mL). However, the predicted 8-week area under the curve (AUC), representing overall drug exposure, was greater for IV infliximab compared to SC infliximab (46,064 μg·hr/mL for IV vs 32,538 μg·hr/mL for SC). Previously reported AUC for SC infliximab and IV infliximab were comparable (28,284 μg·hr/mL for IV vs 35,467 μg·hr/mL for SC).[21] While the AUC for SC infliximab in our study was similar to previous study, the higher AUC for IV infliximab in our study can be attributed to the inclusion of 10 mg/kg dose. In our study, analyzing only the cases where IV infliximab was administered at a dose of 5 mg/kg, the AUC was 34,625 μg·hr/mL, comparable to SC infliximab. Theoretically, if effect of infliximab was dependent on peak concentration, SC infliximab results in lower clinical efficacy. But clinically, most of the patients who switched to SC infliximab demonstrated durable response, similar to the study of Buisson *et al.*,[57] which showed that switching from IV to SC infliximab 120 mg every other week was safe and well accepted, leading to a low risk of relapse in IBD patients. It might be related to lowering ADA and other factors which has not been identified yet. Schreiber *et al.*[21] showed that the overall ADA or neutralizing ADA was lower in SC compared to IV infliximab group. There are several unproven hypotheses.[22] First, the drug level stability of SC dosing may avoid exposure to the more immunogenic concentration thresholds of IV therapy.[21,58] Second, the higher circulating drug levels seen with SC infliximab may both reduce formation of immunogenic drug-antigen immune complexes and induce "high-zone tolerance."[59,60] In "high-zone tolerance," exposure to high concentrations of an antigen may induce tolerance via blunting of the immune response. In our study, 48 patients were treated with more than two times of SC infliximab, and 32 out of 48 patients (66.7%) showed ADA negative conversion after switching to SC infliximab. Interestingly, one patient among 32 patients with ADA negative conversion, showed dramatically decreased ADA from 269 to 7 ng/mL. Factors including the change in formulation and administration intervals which impact TL might contribute to any such differences in immunogenicity.

The strength of our study was the large number of enrolled patients and prospectively collected TLs from real-world clinical settings. And population PK model was developed including clinically important covariates as a relatively simple equation. Regardless of route of administration (IV or SC), present model accurately reflected the PK of infliximab, and validations were proved it. Roblin

et al.[61] showed that SC injection of infliximab resulted in stable drug levels within 2-week treatment cycle in CD patients during the maintenance therapy. Therefore, in inactive CD patients who treated with infliximab SC, infliximab level sampling could be collected at any timepoints during 14-day cycle for infliximab rather than at TL as utilized for IV infliximab. Therefore, our model had advantage for applying very conveniently regardless of IV or SC formulation.

However, our study also had several limitations. First, since our PK model used prospectively collected TLs, based on TDM protocol, the probability that clinical disease course influenced PK mechanisms could not be ruled out. On the other hand, these might be more suitable for clinical application in real-world practice. Second, our study did not evaluate the use of concomitant immunomodulator, as covariate for infliximab CL. It was impossible to make PK model using immunomodulator as a simplified covariate, because of its complexity based on different types, prescribed dosages, and serum levels in individuals (depending on polymorphism, and genotype). Third, since our cohort only included Koreans, the generalization of our findings to IBD patients of other ethnicities is not clear. Fourth, this study included IBD patients with maintenance infliximab therapy. It could not apply to induction infliximab therapy.

We used real-world data from a prospective cohort study to develop population PK model for IV and SC infliximab that predicted infliximab TL during maintenance therapy in patients with IBD. Our final model included BMI, ALB, CRP, and ADA as real-time covariates to predict individual infliximab CL and F.

In conclusion, our study developed the population PK model in patients with IBD who were treated with maintenance infliximab, regardless of route of administration, to predict TL in real-world clinical practice, using BMI, ALB, CRP, and ADA. This model could be used to optimize TL of infliximab, in a way both efficient and tailored optimization for clinical situations. A further study is warranted to verify whether TL has a role with SC infliximab, and to suggest optimal target TL of SC infliximab.

CONFLICTS OF INTEREST

Celltrion provided the Remsima Monitor Drug Level (Immundiagnostik AG, Bensheim, Germany) kit. Except for that, no potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: J.H.S., S.N.H. Data acquisition: M.K., S.K.K. Data analysis and interpretation: J.H.S., M.K., S.K.K., M.G.K. Performance of experiments: M.G.K. Drafting of the manuscript: J.H.S., M.G.K. Critical revision of the manuscript for important intellectual content: S.N.H., M.G.K., E.R.K., D.K.C., Y.H.K. Approval of final manuscript: all authors.

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SUPPLEMENTARY MATERIALS

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REFERENCES

1. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106:644-659.
2. Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. Gastroenterology 2005;128:862-869.
3. Papamichael K, Chachu KA, Vajravelu RK, et al. Improved long-term outcomes of patients with inflammatory bowel disease receiving proactive compared with reactive monitoring of serum concentrations of infliximab. Clin Gastroenterol Hepatol 2017;15:1580-1588.

4. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. Gastroenterology 2014;147:1296-1307.
5. Papamichael K, Vande Casteele N, Jeyarajah J, Jairath V, Osterman MT, Cheifetz AS. Higher postinduction infliximab concentrations are associated with improved clinical outcomes in fistulizing Crohn's disease: an ACCENT-II post hoc analysis. Am J Gastroenterol 2021;116:1007-1014.
6. Cornillie F, Hanauer SB, Diamond RH, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut 2014;63:1721-1727.
7. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol 2019;4:341-353.
8. Na SY, Choi CH, Song EM, et al. Korean clinical practice guidelines on biologics and small molecules for moderate-to-severe ulcerative colitis. Intest Res 2023;21:61-87
9. Koh SJ, Hong SN, Park SK, et al. Korean clinical practice guidelines on biologics for moderate to severe Crohn's disease. Intest Res 2023;21:43-60.
10. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015;148:1320-1329.
11. Vande Casteele N, Khanna R, Levesque BG, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. Gut 2015;64:1539-1545.
12. Dotan I, Ron Y, Yanai H, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. Inflamm Bowel Dis 2014;20:2247-2259.
13. Yarur AJ, McGovern D, Abreu MT, et al. Combination therapy with immunomodulators improves the pharmacokinetics of infliximab but not vedolizumab or ustekinumab. Clin Gastroenterol Hepatol 2023;21:2908-2917.
14. Li Wai Suen CFD, Choy MC, De Cruz P. What to do when traditional rescue therapies fail in acute severe ulcerative colitis. Intest Res 2024;22:397-413.
15. Brandse JF, Mathôt RA, van der Kleij D, et al. Pharmacokinetic features and presence of antidrug antibodies associate with response to infliximab induction therapy in patients with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol 2016;14:251-258.
16. Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther 2011;33:946-964.
17. Brandse JF, Mould D, Smeekes O, et al. A real-life population pharmacokinetic study reveals factors associated with clearance and immunogenicity of infliximab in inflammatory bowel disease. Inflamm Bowel Dis 2017;23:650-660.
18. Gibson DJ, Ward MG, Rentsch C, et al. Review article: determination of the therapeutic range for therapeutic drug monitoring of adalimumab and infliximab in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2020;51:612-628.
19. Ye BD, Pesegova M, Alexeeva O, et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study. Lancet 2019;393:1699-1707.
20. Gros B, Plevris N, Constantine-Cooke N, et al. Multiple infliximab biosimilar switches appear to be safe and effective in a real-world inflammatory bowel disease cohort. United European Gastroenterol J 2023;11:179-188.
21. Schreiber S, Ben-Horin S, Leszczyszyn J, et al. Randomized controlled trial: subcutaneous vs intravenous infliximab CT-P13 maintenance in inflammatory bowel disease. Gastroenterology 2021;160:2340-2353.
22. Little RD, Ward MG, Wright E, et al. Therapeutic drug monitoring of subcutaneous infliximab in inflammatory bowel disease-understanding pharmacokinetics and exposure response relationships in a new era of subcutaneous biologics. J Clin Med 2022;11:6173.
23. Hong SN, Song JH, Kim SJ, et al. One-year clinical outcomes of subcutaneous infliximab maintenance therapy compared with intravenous infliximab maintenance therapy in patients with inflammatory bowel disease: a prospective cohort study. Inflamm Bowel Dis 2024;30:517-528.
24. Lee B, Kim M, Kim ER, Hong SN, Chang DK, Kim YH. Effectiveness of switching to subcutaneous infliximab in inflammatory bowel disease patients with inadequate biochemical response during intravenous administration. Sci Rep 2024;14:24347.
25. Elford AT, Heldt R, Kamal S, Christensen B, Segal JP. Systematic review with meta-analysis of the effectiveness of subcutaneous biologics versus intravenous biologics in inflammatory bowel diseases. Eur J Gastroenterol Hepatol 2025;37:47-54.
26. Chetwood JD, Tran Y, Subramanian S, et al. Intravenous versus subcutaneous infliximab in inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis 2024;18:1440-1449.
27. Buisson A, Nachury M, Bazoge M, et al. Long-term effectiveness and acceptability of switching from intravenous to subcutaneous infliximab in patients with inflammatory bowel

disease treated with intensified doses: the REMSWITCH-LT study. Aliment Pharmacol Ther 2024;59:526-534.
28. Kim JH, Han N, Kim MG, et al. Model based development of tacrolimus dosing algorithm considering CYP3A5 genotypes and mycophenolate mofetil drug interaction in stable kidney transplant recipients. Sci Rep 2019;9:11740.
29. Hanzel J, Bukkems LH, Gecse KB, D'Haens GR, Mathôt RA. Population pharmacokinetics of subcutaneous infliximab CT-P13 in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther 2021;54:1309-1319.
30. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541-1549.
31. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383-1395.
32. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of response to anti-TNFs: definition, epidemiology, and management. Clin Transl Gastroenterol 2016;7:e135.
33. Kopylov U, Ben-Horin S, Seidman E. Therapeutic drug monitoring in inflammatory bowel disease. Ann Gastroenterol 2014;27:304-312.
34. Ordás I, Rimola J, Alfaro I, et al. Development and validation of a simplified magnetic resonance index of activity for Crohn's disease. Gastroenterology 2019;157:432-439.
35. Roseira J, Ventosa AR, de Sousa HT, Brito J. The new simplified MARIA score applies beyond clinical trials: a suitable clinical practice tool for Crohn's disease that parallels a simple endoscopic index and fecal calprotectin. United European Gastroenterol J 2020;8:1208-1216.
36. Klenske E, Bojarski C, Waldner M, Rath T, Neurath MF, Atreya R. Targeting mucosal healing in Crohn's disease: what the clinician needs to know. Therap Adv Gastroenterol 2019;12:1756284819856865.
37. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505-512.
38. Song JH, Hong SN, Kim ER, Chang DK, Kim YH. 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. Medicine (Baltimore) 2022;101:e30683.
39. Immundiagnostik AG. Remsima® Monitor drug level, for the determination of free Remsima® concentration in EDTA plasa and serum. Immundiagnostik AG; 2018.
40. Zoghbi J, Xu Y, Grabert R, Theobald V, Richards S. A breakthrough novel method to resolve the drug and target interference problem in immunogenicity assays. J Immunol Methods 2015;426:62-69.
41. Roblin X, Nancey S, Papamichael K, et al. Higher serum infliximab concentrations following subcutaneous dosing are associated with deep remission in patients with inflammatory bowel disease. J Crohns Colitis 2024;18:679-685.
42. Fasanmade AA, Adedokun OJ, Olson A, Strauss R, Davis HM. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. Int J Clin Pharmacol Ther 2010;48:297-308.
43. Adedokun OJ, Xu Z, Liao S, et al. Population pharmacokinetics and exposure-response modeling of golimumab in adults with moderately to severely active ulcerative colitis. Clin Ther 2020;42:157-174.
44. Rosario M, Dirks NL, Gastonguay MR, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. Aliment Pharmacol Ther 2015;42:188-202.
45. Kumar P, Vuyyuru SK, Das P, et al. Serum albumin is the strongest predictor of anti-tumor necrosis factor nonresponse in inflammatory bowel disease in resource-constrained regions lacking therapeutic drug monitoring. Intest Res 2023;21:460-470.
46. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology 2015;149:350-355.
47. Buurman DJ, Maurer JM, Keizer RJ, Kosterink JG, Dijkstra G. Population pharmacokinetics of infliximab in patients with inflammatory bowel disease: potential implications for dosing in clinical practice. Aliment Pharmacol Ther 2015;42:529-539.
48. Lichtenstein GR, McGovern DP. Using markers in IBD to predict disease and treatment outcomes: rationale and a review of current status. Am J Gastroenterol Suppl 2016;3:17-26.
49. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology 2021;160:1570-1583.
50. Song JH, Hong SN, Lee JE, et al. C-reactive protein reduction rate following initiation of anti-tumor necrosis factor α induction therapy predicts secondary loss of response in patients with Crohn's disease. Scand J Gastroenterol 2019;54:876-885.
51. Kopylov U, Seidman E. Predicting durable response or resistance to antitumor necrosis factor therapy in inflammatory bowel disease. Therap Adv Gastroenterol 2016;9:513-526.
52. Deyhim T, Cheifetz AS, Papamichael K. Drug clearance in patients with inflammatory bowel disease treated with bio-

logics. J Clin Med 2023;12:7132.
53. Chung A, Carroll M, Almeida P, et al. Early infliximab clearance predicts remission in children with Crohn's disease. Dig Dis Sci 2023;68:1995-2005.
54. Davis JD, Bravo Padros M, Conrado DJ, et al. Subcutaneous administration of monoclonal antibodies: pharmacology, delivery, immunogenicity, and learnings from applications to clinical development. Clin Pharmacol Ther 2024;115:422-439.
55. Thomas VA, Balthasar JP. Understanding inter-individual variability in monoclonal antibody disposition. Antibodies (Basel) 2019;8:56.
56. Vermeire S, Dreesen E, Papamichael K, Dubinsky MC. How, when, and for whom should we perform therapeutic drug monitoring? Clin Gastroenterol Hepatol 2020;18:1291-1299.
57. Buisson A, Nachury M, Reymond M, et al. Effectiveness of switching from intravenous to subcutaneous infliximab in patients with inflammatory bowel diseases: the REM-SWITCH study. Clin Gastroenterol Hepatol 2023;21:2338-2346.
58. Smith PJ, Critchley L, Storey D, et al. Efficacy and safety of elective switching from intravenous to subcutaneous infliximab [CT-P13]: a multicentre cohort study. J Crohns Colitis 2022;16:1436-1446.
59. Janeway CA. Immunobiology: the immune system in health and disease. 5th ed. New York: Garland Publishing, 2001.
60. Schreiber S, Jang BI, Borzan V, et al. Novel formulation of CT-P13 (infliximab biosimilar) for subcutaneous administration: initial results from a phase I open-label randomized controlled trial in patients with active Crohn's disease. Gastroenterology 2018;154(6 Suppl 1):S-1371.
61. Roblin X, Veyrard P, Bastide L, et al. Subcutaneous injection of infliximab CT-P13 results in stable drug levels within 14-day treatment cycle in Crohn's disease. Aliment Pharmacol Ther 2022;56:77-83.