의학석사 학위논문

국내 크론병 환자에서 정맥 투여 후 Infliximab 농도에 대한 집단 약동학 모형

Population Pharmacokinetic Model of Intravenous Infliximab in Korean Patients with Crohn's Disease

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이 문 희

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지 도 교 수　　배　균　섭

이 논문을 의학석사 학위 논문으로 제출함

2024년　8월

울 산 대 학 교 대 학 원

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Abstract

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Background: Infliximab is a chimeric monoclonal antibody that binds and neutralizes tumor necrosis factor alpha. Since 1998, it has been approved for several autoimmune diseases, including inflammatory bowel disease. The relationship between infliximab exposure and treatment response varies among patients.

Purpose: This study aimed to establish a population pharmacokinetic model of intravenous infliximab in Korean patients with Crohn's disease.

Methods: We performed a retrospective, single-center analysis of data from 100 patients with Crohn's disease who received scheduled induction and maintenance therapy at Asan Medical Center, a university hospital in Korea. A population pharmacokinetic model was developed using NONMEM®, and demographic, clinical, and laboratory data were tested to establish covariates of infliximab pharmacokinetics.

Results: One-compartment pharmacokinetic model with first-order elimination best described the serum infliximab concentration measurements. Population pharmacokinetic parameter estimates were 0.012 L/h for clearance (CL) (95% confidence interval: 0.012 - 0.013 L/h) and 6.301 L for the volume of distribution (V) (95% confidence interval: 5.932 - 6.671 L). Covariate analysis showed that CL and V increased as body weight increased. CL was higher in patients with low serum albumin, high serum C-reactive protein, and increasing age, with differing coefficients for each covariate.

Conclusions: Our population pharmacokinetic model suggests that the disposition of infliximab is affected by body weight, age, C-reactive protein, and serum albumin levels in Korean patients with Crohn's disease.

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Abbreviations

ALB	albumin
ATI	antibodies to infliximab
BSA	body surface area
BWT	body weight
CDAI	Crohn's disease activity index
CI	confidence interval
CL	clearance
COV	covariance
CRP	C-reactive protein
CWRES	conditional weighted residual
DV	dependent variable
FC	fecal calprotectin
HBI	Harvey-Bradshaw index
IBD	inflammatory bowel disease
IMM	immunomodulator
IPRE	individual prediction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRED	population predication
Q	intercompartmental clearance
RSE	relative standard error
V	volume of distribution
Vc	volume of distribution in the central compartment
Vp	volume of distribution in the peripheral compartment
WBC	white blood cell count
5-ASA	5-aminosalicyclic acid

Introduction

Infliximab is a chimeric monoclonal antibody to tumor necrosis factor-α approved for use in Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. It is administered by intravenous infusion at 0, 2, and 6 weeks for induction therapy, followed by maintenance therapy at six- to eight-week intervals. The dosage and maintenance dosing interval depends on the disease being treated.[1)]

Serum concentration of infliximab has large inter-individual variability. The clearance of infliximab seems to be affected by several factors. Although infliximab has been used for more than a decade, the factors that influence the pharmacokinetics of infliximab have not been fully investigated.

Serum trough level of infliximab is known to be closely related to the efficacy of infliximab. Serum infliximab concentration was associated with treatment efficacy in patients with rheumatoid arthritis and ulcerative colitis.[2-5)]

In patients with Crohn's disease, infliximab trough levels were associated with treatment response, and the risk of treatment failure was lower when infliximab trough level was greater than 3 ug/mL.[6,7)] Low serum infliximab trough levels are associated with increased C-reactive protein levels. Low infliximab trough concentration and antibodies to infliximab (ATI) are associated with poor clinical outcomes in patients with Crohn's disease. Infliximab trough concentrations greater than 2.79 ug/mL and ATI concentrations less than 3.15 IU/mL were reported as independent predictors of remission.[8)] High serum infliximab trough levels during the induction period are associated with higher mucosal healing rates. More importantly, loss of response to infliximab is often attributed to low trough levels.

Therapeutic drug monitoring can improve treatment outcomes in patients treated with infliximab. To adequately perform therapeutic drug monitoring, a pharmacokinetic (PK) model is necessary. Evaluation of pharmacokinetic characteristics of intravenous infliximab in Korean patients with Crohn's disease has not been performed previously. We aimed to develop

a population pharmacokinetic model for intravenous infliximab in Korean patients with Crohn's disease and thereby identify the demographics or biomarkers that are predictive of pharmacokinetics.

Methods

1. Data collection

We retrospectively analyzed data of Crohn's disease patients treated with intravenous infliximab from April 2019 to March 2022 at Asan Medical Center, a university hospital. All patients had an established diagnosis of Crohn's disease with moderate to severe disease activity. The treatment regimen followed the recommendation for Crohn's disease with induction doses of 5 mg/kg at 0, 2, and 6 weeks, followed by maintenance doses of 5-10 mg/kg every 8 weeks. Approval from the institutional review board was acquired prior to data collection.

Data related to infliximab administration, such as date and time of dosing, duration of infusion, and drug amount, were collected from the electronic medical record. Serum infliximab concentrations (ug/mL) determined from a validated enzyme-linked immunosorbent assay (Seoul Clinical Laboratories) were also collected from the electronic medical record.

Demographic data such as age, sex, body weight, and height were collected to be evaluated as potential covariates. Clinical laboratory covariates were serum creatinine (mg/dL), estimated glomerular filtration rate (mL/min/1.73 m^2), albumin (g/dL), hemoglobin (g/dL), hematocrit (%), white blood cell, lymphocyte, and platelet counts (10^9/L), erythrocyte sedimentation rate, and C-reactive protein (mg/dL). Additional covariates were fecal calprotectin (ug/mg) and Crohn's disease activity index (CDAI) score.

2. Population pharmacokinetic model

A population PK model was developed using the full dosing data and concentration measurements of the patients. One, two, and three-compartment models with first-order absorption and first-order elimination were explored to develop the base model. The Akaike information criteria and goodness-of-fit plots were used to compare these structural models.

Additive, proportional, and combined error models were tested in the selected base model.

3. Covariate analysis

For covariate selection, covariate screening, forward selection, and backward elimination were adopted with a significance level of p=0.05. Empirical Bayes estimates were graphically explored to screen for relationships between PK parameters and potential covariates. Candidate covariates were added to the model using the following functions.

continuous covariate:

$$\text{Parameter} = \text{typical value of parameter} \cdot \left(\frac{covariate}{median\ value\ of\ covariate}\right)^{theta}$$

categorical covariate:

$$\text{Parameter} = \text{typical value of parameter} \cdot (theta)^{covariate}$$

The appropriateness of covariate selection was determined by the log-likelihood ratio test as the primary criterion. Individual covariates were added until there was no significant reduction in the objective function value.

4. Model evaluation

The final model was chosen from candidate models in which both the minimization and covariance (standard error) steps were successful. Diagnostic plots were reviewed for successful models to see how well the model fitted observed data. Residuals and parameter precision were also examined. The objective function value was the main criterion for final model selection.

5. Software

Data preparation and plot generation were performed using R version 4.1.2 or higher (http://cran.r-project.org/). For nonlinear mixed effects modeling, NONMEM® version 7.5 (ICON plc) was used to build the population pharmacokinetic model.

Results

1. Study population

The analysis included one hundred patients who received intravenous infliximab treatment and had serum infliximab concentration. The study population consisted of 72 males (72%) and 28 females (28%). Baseline characteristics of the 100 patients included in the analysis are summarized in **Table 1**. The median body weight was 65.6 kg (range 33.0 - 102.3 kg), and the median age was 27 years (range 17 - 77 years). Thirty-seven patients had previously received bowel resection surgery. No patient had detectable antibodies to infliximab. A total of 823 serum infliximab concentration data were collected and analyzed for nonlinear mixed effects modeling.

2. Population pharmacokinetic model

The serum infliximab concentration measurements were best described by a one-compartment population PK model with first-order elimination. Population PK estimates were 0.012 L/h for clearance (CL) (95% confidence interval: 0.012 - 0.013 L/h) and 6.301 L for the volume of distribution (V) (95% confidence interval: 5.932 - 6.671 L).

The covariate analysis showed that CL and V increased as body weight increased. CL was higher in patients with low serum albumin, high serum C-reactive protein, and increasing age, with differing coefficients for each covariate. Equations for the final covariate model of intravenous infliximab in Korean patients with Crohn's disease are shown in **Figure 1**.

Table 1. Baseline characteristics

Baseline characteristics	Study patients (n=100)
Sex	
Female	28 (28.0%)
Male	72 (72.0%)
Smoking status	
Never smoked	71 (71.0%)
Previous smoker	8 (8.0%)
Current smoker	21 (21.0%)
Family history	
No family history	90 (90.0%)
IBD in first degree relatives	10 (10.0%)
Disease location	
L1 (ileal)	17 (17.0%)
L2 (colonic)	5 (5.0%)
L3 (ileocolonic)	78 (78.0%)
Disease behavior	
B1 (inflammatory)	50 (50.0%)
B2 (stricturing)	15 (15.0%)
B3 (penetrating)	35 (35.0%)
History of previous biologic use	
Absent	96 (96.0%)
Present	4 (4.0%)
History of previous bowel resection	
Absent	63 (63.0%)
Present	37 (37.0%)
History of perianal fistula/abscess	
Absent	44 (44.0%)
Present	56 (56.0%)
Concomitant use of an immunomodulator	
No	17 (17.0%)
Yes	83 (83.0%)
Concomitant use of 5-ASA	
No	48 (48.0%)
Yes	52 (52.0%)
Concomitant use of corticosteroids	
No	52 (52.0%)
Yes	48 (48.0%)

IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid

$$\mathrm{CL} = 0.012 \cdot \left(\frac{BWT}{65}\right)^{0.503} \cdot \left(\frac{ALB}{4.1}\right)^{-0.645} \cdot \left(\frac{CRP}{0.1}\right)^{0.03} \cdot \left(\frac{AGE}{27}\right)^{0.203}$$

$$\mathrm{V} = 6.301 \cdot \left(\frac{BWT}{65}\right)^{0.36}$$

AGE, age (years); ALB, albumin (g/dL); BWT, body weight (kg); CL, clearance (L/h); CRP, C-reactive protein (mg/dL); V, volume of distribution (L)

Figure 1. Equations for the final population pharmacokinetic model of intravenous infliximab in Korean patients with Crohn's disease

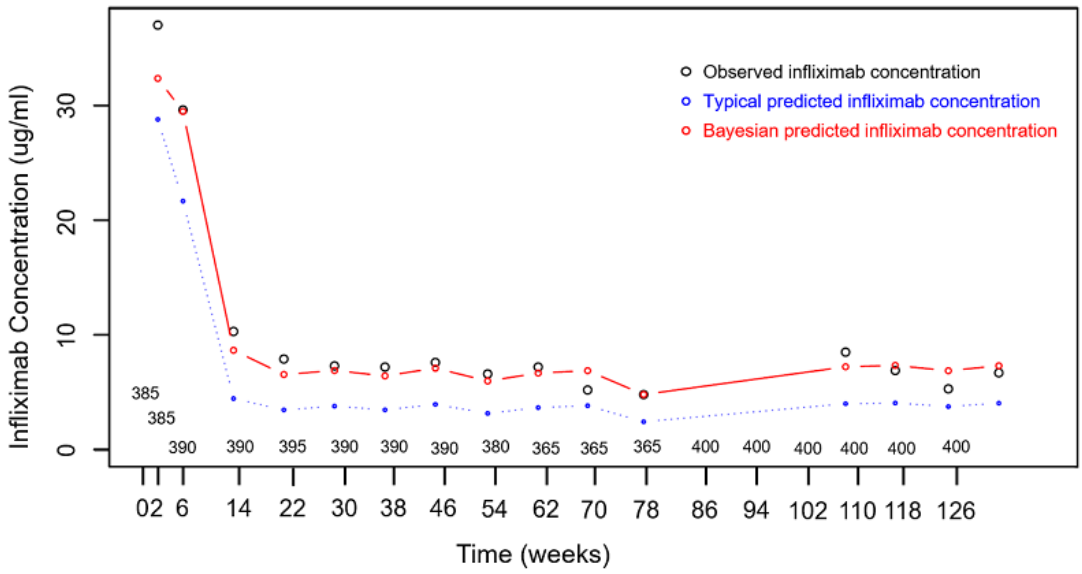
The percent relative standard errors (% RSE) show that the parameters were estimated with good precision (**Table 2**).

Table 2. Population pharmacokinetic parameter estimates (n=100)

Parameter	Estimate	% RSE	95% CI
CL (L/h)	0.012	2.7	0.012 ~ 0.013
V (L)	6.301	2.9	5.932 ~ 6.671
θ_{BWT_CL} (power of body weight on CL)	0.503	23.4	0.268 ~ 0.738
θ_{Alb_CL} (power of albumin on CL)	-0.645	14.6	-0.834 ~ -0.456
θ_{CRP_CL} (power of C-reactive protein on CL)	0.030	20.1	0.018 ~ 0.043
θ_{Age_CL} (power of age on CL)	0.203	36.5	0.055 ~ 0.351
θ_{BWT_V} (power of body weight on V)	0.360	37.5	0.090 ~ 0.629
ω_{CL}^2	0.037	21.7	-
ω_{V}^2	0.002	506.6	-
COV(η_{CL}, η_{V})	-0.004	187.7	-
Additive error (ug/ml), σ_{add}	0.209	26.0	-
Proportional error, σ_{prop}	0.213	4.5	-

CI, confidence interval; CL, clearance; COV, covariance; RSE, relative standard error; V, volume of distribution

Evaluation of individual plots revealed that the final covariate model predicted the observed concentration-time profiles of infliximab reasonably well. **Figure 2** shows observed and model-predicted concentration-time profiles in an exemplary patient who received 5 mg/kg infliximab throughout the study period and who was not positive for anti-drug antibodies to infliximab.



Numbers within the graph are dosing amounts (mg).

Figure 2. Observed and model-predicted concentration-time profiles in an exemplary patient

3. Model validation

Goodness-of-fit plots for the final model showed good correlation between observed and predicted values for population prediction (PRED) and individual prediction (IPRE) as shown in **Figure 3**.

Evaluation of the conditional weighted residuals showed the appropriateness of the model as shown in **Figure 4**.

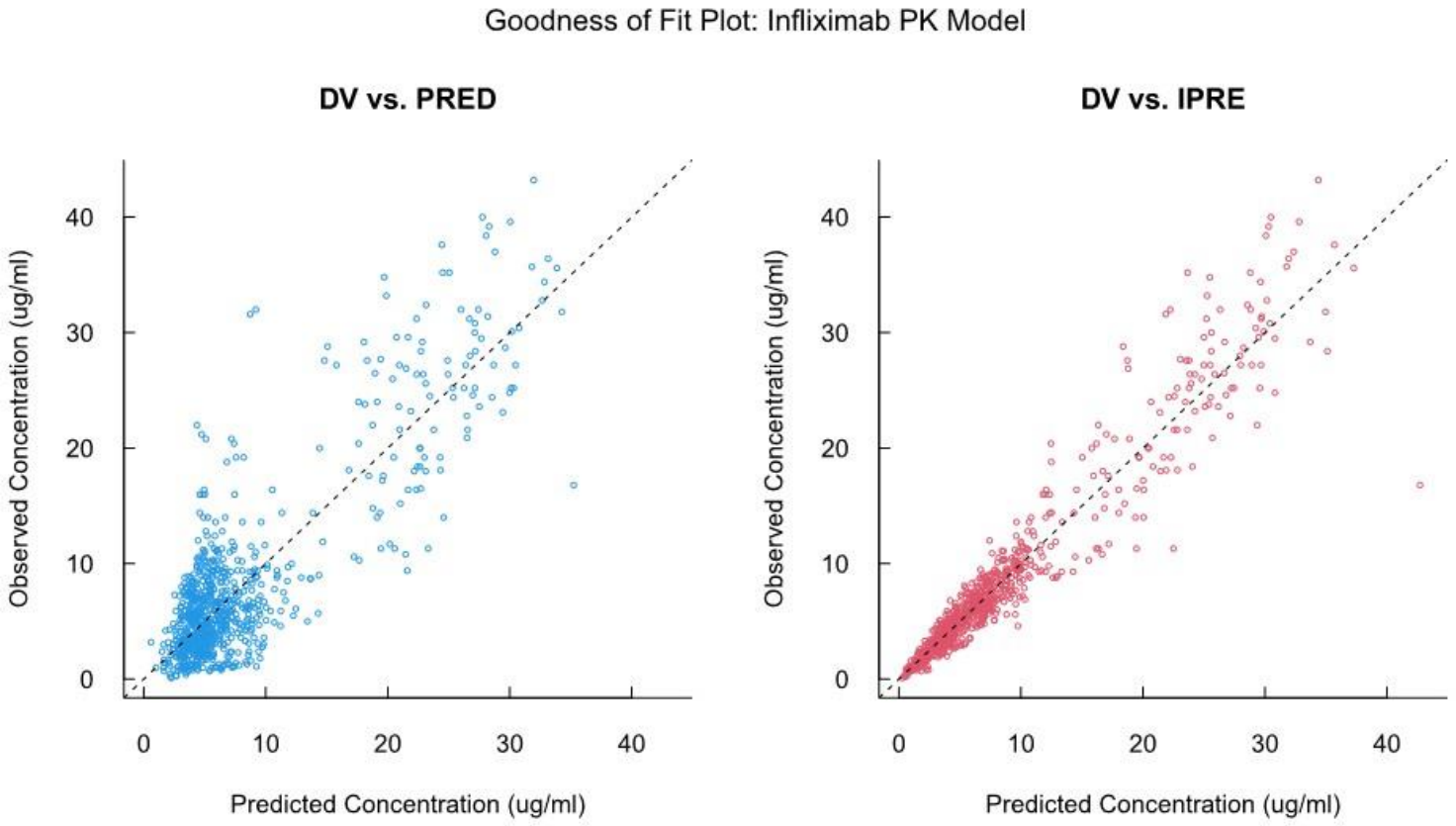


Figure 3. Goodness of fit plots for the final model

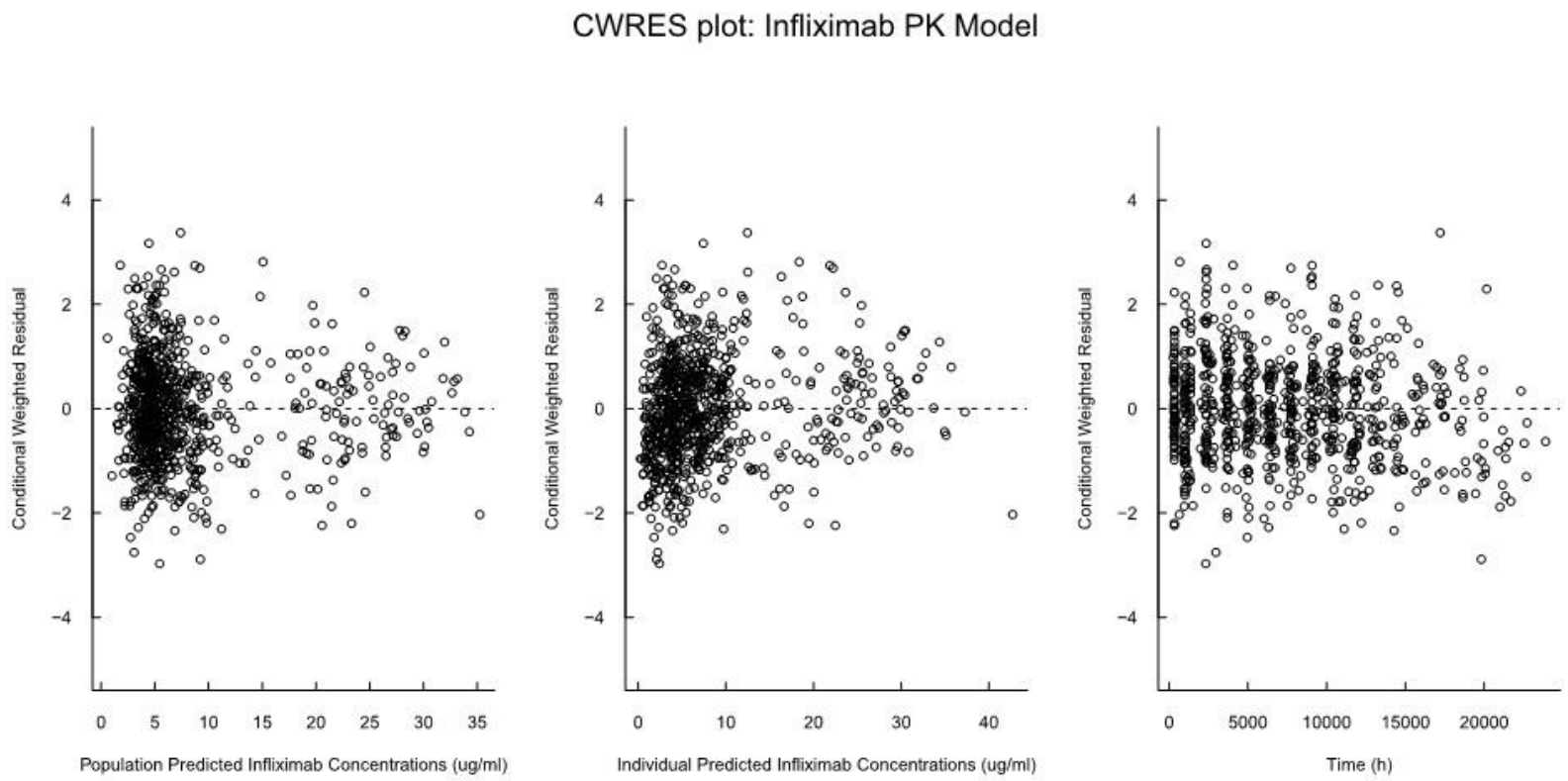


Figure 4. Conditional weighted residuals of the final model

Discussion

This study is the first evaluation of the population pharmacokinetics of infliximab in Korean patients with Crohn's disease. Our study identified C-reactive protein as a predictor of clearance. This finding was not previously reported in earlier analyses of infliximab PK. Because the power for C-reactive protein was determined to be a small number (0.03), when C-reactive protein increases a hundredfold from 0.1 mg/dL to 10 mg/dL, clearance increases 1.15 times. Normalization of elevated baseline C-reactive protein after infliximab treatment was associated with favorable long-term outcomes.[9,10)]

According to our model, clearance of infliximab increased with a decrease in serum albumin concentration. This finding is consistent with the results of previous studies. Fasanmade et al analyzed the pharmacokinetic properties of infliximab in children and adults with Crohn's disease based on data from phase 3 clinical trials.[11)] In that analysis, clearance was higher in children and adults with low baseline serum albumin concentration. In a study on patients with ulcerative colitis, lower serum albumin concentration was associated with lower serum infliximab concentration and lower response rates.[3)]

In our study, weight was found to influence infliximab PK. This finding is consistent with the results of other studies.[11,12)]

The patients in our study ranged in age from 17 to 77 years. Although pediatric patients were not included, age was found to influence infliximab PK in our study.

Our study tested the Crohn's disease activity index score but found no significant impact on infliximab clearance.

The earlier models for infliximab identified different biomarkers as the factors that influence infliximab PK (**Table 3**).[11-16)]

Table 3. Population pharmacokinetic models of infliximab

Year	Author	Disease	N	Half-life (days)	Parameter estimates ± standard error	Between-subject variability	Covariates
2008	Xu et al [13]	Ankylosing spondylitis	274		CL: 0.273 ± 0.007 L/d Vc: 3.06 ± 0.0057 L Q: 1.72 ± 0.48 L/d Vp: 2.94 ± 0.17 L	CL 34.1 % Vc 17.5 %	CL: ATI, WBC Vc: SEX, BSA
2008	Ternant et al [14]	Inflammatory bowel disease	33	18.5			CL: ATI Vc: BWT, SEX
2009	Fasanmade et al [12]	Ulcerative colitis	482	14	CL: 0.407 ± 0.0103 L/d Vc: 3.29 ± 0.0679 L Q: 7.14 ± 0.489 L/d Vp: 4.13 ± 0.16 L	CL 37.7 % Vc 22.1 %	CL: ALB, ATI, SEX Vc: BWT, SEX
2011	Fasanmade et al [11]	Crohn's disease	692	adults: 12.4 children: 13.2	CL: 5.39 ± 0.13 mL/kg/d Vc: 52.7 ± 0.49 mL/kg Q: 2.15 ± 0.39 mL/kg/d Vp: 19.0 ± 1.53 mL/kg		CL: ATI, ALB, IMM, BWT V: BWT
2015	Buurman et al [15]	Inflammatory bowel disease	42		CL: 0.199 L/d Vc: 4.94 L Q: 0.0618 L/day Vp: 3.13 L		CL: ATI, SEX, Period V: HBI
2020	Dreesen et al [16]	Crohn's disease	116		CL: 0.277 L/d Vc: 4.90 L Q: 0.0201 L/day Vp: 0.844 L	CL 28.5 %	CL: ATI, ALB, FC, CDAI
2024	This study	Crohn's disease	100		CL: 0.012 L/h V: 6.301 L	CL 19.4 % V 4.5 %	CL: BWT, ALB, CRP, AGE V: BWT

AGE, age; ALB, albumin; ATI, antibody to infliximab; BSA, body surface area; BWT, body weight; CDAI, Crohn's disease activity index; CL, clearance; FC, fecal calprotectin, HBI, Harvey-Bradshaw index; IMM, immunomodulator; N, number of patients; Vc, volume of distribution in the central compartment; Vp, volume of distribution in the peripheral compartment; Q, intercompartmental clearance; WBC, white blood cell count.

In other studies, antibodies to infliximab were associated with increased infliximab clearance. However, patients in our study did not have antibodies to infliximab. Antibodies to infliximab were reported to contribute to inadequate response to treatment.

In some studies, sex was found to influence infliximab PK in patients with ulcerative colitis.[12] However, sex was not found to affect infliximab PK in our study.

There are several limitations of our study. In previous studies of infliximab population PK modeling, two-compartment models were suggested.[11-16] However, one-compartment model best described the infliximab concentration data in our study. Since our study used retrospectively collected data which mostly consisted of trough concentration, data may not have been insufficient to capture the multiple compartments. In addition, the kit used to measure infliximab concentration in our study was developed for therapeutic drug monitoring of trough concentrations, which may be associated with suboptimal measurements of peak concentrations.

Lower clearance and longer half-life were associated with the response rates after induction therapy as well as steroid-free remission rates after maintenance therapy in ulcerative colitis patients.[17] Primary non-responders to infliximab in Crohn's disease were reported to be 10.9 % and loss of response was observed in 21.6 % of responders.[9]

Various optimization strategies based on therapeutic drug monitoring have been suggested to manage the infliximab concentration levels within the therapeutic window. The superiority of Bayesian dashboard guided dosing over standard regimen has been shown during induction and maintenance.[18,19] Such optimization strategies demand valid pharmacokinetic model of intravenous infliximab.

Our population PK model may be used to perform therapeutic drug monitoring more accurately and optimize infliximab treatment in Korean patients with Crohn's disease. Simulation studies based on our model may generate useful information regarding the optimal dosing regimen of infliximab according to patient characteristics. Further development of our

model into a population PK-PD model that characterizes the infliximab dose-exposure-response relationship will allow for model-based infliximab dose optimization. This may improve treatment outcomes in Korean patients with Crohn's disease.

Conclusion

We established a population PK model of intravenous infliximab in Korean patients with Crohn's disease. This is the first population PK model of intravenous infliximab in the South Korean population. The final covariate model showed that infliximab clearance is affected by serum albumin, C-reactive protein, body weight, and age. Our study offers a baseline population PK model for future studies to optimize intravenous infliximab treatment.

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Appendix

Appendix 1. NONMEM code for population pharmacokinetic model

```
$PROB Infliximab IV Infusion P:101 F:CL~BWT+Alb+CRP+AGE,V1~BWT
$INPUT ID DAT2=DROP TIME AMT RATE CMT SS II MDV DV SEX BWT HT AGE
       CDAI FC ESR eGFR Alb Cr CRP LYM WBC Hb Hct PLT
$DATA ../infliximab_0722.csv IGNORE=@
$SUBR ADVAN1 TRANS2
$ABBR DERIV2=NO

$PK
  TVCL = THETA(1)*(BWT/65)**THETA(5)*(Alb/4.1)**THETA(7)*(CRP/0.1)**THETA(8)*(AGE/27)**THETA(9)
  TVV  = THETA(2)*(BWT/65)**THETA(6)
  CL   = TVCL*EXP(ETA(1))
  V    = TVV *EXP(ETA(2))
  K    = CL/V
  HALF = LOG(2)/K
  S1   = V

$ERROR
  IPRE = F
  W    = SQRT(THETA(3)**2 + THETA(4)**2*IPRE**2)
  IRES = DV - IPRE
  IWRE = IRES / W
  Y    = IPRE + W * EPS(1)

$THETA
  (0, 0.01)         ; CL
  (0, 6)            ; V

  (1e-8, 30, 100)   ; Additive
  (1e-8, 0.2, 1)    ; Proportional

  (0, 0.5)          ; BWT
  (0, 0.5)          ; BWT

  (1)               ; Alb
  (0, 0.1, 30)      ; CRP
  (1e-8, 1, 30)     ; AGE

$OMEGA BLOCK(2)
  0.2
  0.1 0.2

$SIGMA 1 FIX
$EST MAX=9999 PRINT=5 METHOD=COND INTER MSFO=THIS.MSF
     NOABORT NOTBT NOOBT NOSBT
$COV UNCOND PRINT=ERS
$TAB ID TIME MDV IPRE IWRE CWRES
     FILE=sdtab NOPRINT ONEHEADER FORMAT=s1PE16.8
$TAB ID CL V K HALF
     ETA(1) ETA(2)
     FILE=patab NOPRINT ONEHEADER NOAPPEND FORMAT=s1PE16.8
$TAB ID BWT HT AGE
     FILE=cotab NOPRINT ONEHEADER NOAPPEND FORMAT=s1PE16.8
$TAB ID SEX
     FILE=catab NOPRINT ONEHEADER NOAPPEND FORMAT=s1PE16.8
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국문요약

인플릭시맙은 종양괴사인자 알파(tumor necrosis factor-alpha)에 결합하여 중화시키는 키메라 단일클론항체이다. 인플릭시맙은 1998년부터 염증성 장질환(inflammatory bowel disease)을 포함하여 여러가지 자가면역질환의 치료제로 승인되었는데, 인플릭시맙의 노출과 치료 반응의 관계는 환자에 따라 다르게 나타난다.

이에 본 연구는 한국인 크론병 환자를 대상으로 정맥 인플릭시맙의 집단 약동학 모형을 구축하는 것을 목표로 하였다.

국내 대학병원인 서울아산병원에서 예정된 유도 및 유지 요법을 받은 크론병 환자 100명의 데이터를 후향적 단일 센터 분석을 수행하였다. NONMEM® version 7.5를 사용하여 집단 약동학 모형을 개발하고 인구 통계학, 임상 및 실험실 데이터를 테스트하여 인플릭시맙 약동학의 공변량을 설정하였다.

First-order elimination을 가지는 1구획 PK 모형이 관찰된 혈청 인플릭시맙 농도를 가장 잘 설명하였다. 집단 약동학적 변수는 청소율(clearance, CL)의 경우 0.012 L/h (95% 신뢰 구간: 0.012 - 0.013 L/h), 분포 용적(volume of distribution, V)의 경우 6.301 L (95% 신뢰 구간: 5.932 - 6.671 L)로 추정되었다. 공변량 분석 결과, 체중이 증가함에 따라 청소율과 분포 용적이 증가하는 것으로 나타났다. 청소율은 혈청 알부민이 낮은 경우와, 혈청 C-반응성 단백질(C-reactive protein)이 높은 경우 및 환자 나이가 증가할 수록 더 높았으며, 각 공변량에 대한 계수들의 추정치는 아래의 수식과 같았다.

$$\mathrm{CL} = 0.012 \cdot \left(\frac{BWT}{65}\right)^{0.503} \cdot \left(\frac{ALB}{4.1}\right)^{-0.645} \cdot \left(\frac{CRP}{0.1}\right)^{0.03} \cdot \left(\frac{AGE}{27}\right)^{0.203}$$

$$\mathrm{V} = 6.301 \cdot \left(\frac{BWT}{65}\right)^{0.36}$$

AGE, 나이 (years); ALB, 알부민 (g/dL); BWT, 체중 (kg); CL, 청소율 (L/h); CRP, C-반응성 단백질 (mg/dL); V, 분포 용적 (L)

본 연구는 한국인 염증성 장질환 환자에서 정맥 투여 후 인플릭시맙의 농도에 대한 집단 약동학 모형을 구축한 최초로 연구로서, 한국인 크론병 환자에서 인플릭시맙의 disposition이 체중, 연령, C-반응성 단백질 및 혈청 알부민 수치에 영향을 받는다는 것을 제시하였다.

실제 치료 목적으로 인플릭시맙을 투약 받고 있는 환자의 농도 데이터를 이용하여 약동학 모형을 구축하였으므로 실제 환자의 약동학적 특성을 반영하는 연구이며, 향후 후속 개발을 통해 한국인 염증성 장질환 환자에서 인플릭시맙의 최적 용량 및 용법을 설정하고 평가하는데 활용할 수 있는 유용한 정보를 제시하고 있다.