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Application of Bayesian Modeling with Infliximab to Determine Optimal Patient Specific Regimen

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Introduction

Infliximab (IFX), a chimeric monoclonal IgG1 anti-TNF-alpha antibody, is often used to treat inflammatory bowel disease (IBD), particularly if non-biologic treatments have failed. Individualization of IFX dosing to optimize clinical response is desired with an acceptable target trough serum concentration of ≥5 µg/mL, yet application of therapeutic drug monitoring (TDM) if often difficult due to significant patient variability.[1]

To assist clinicians with individualized IFX dosing, a Bayesian pharmacokinetic dosing was applied to real world patients and analyzed using 2 previously published models.[2,3]

Methods

A retrospective review of electronic medical records of adult IBD pts treated with IFX in 2 large U.S. gastroenterology private practice infusion centers.

Study Cohort:

All patients with at least 2 IFX serum concentrations and 2 IFX doses prior to TDM

Data collection:

- demographics (age, gender, weight, disease type)
- IFX treatment regimen
- IFX concentration data, dosing dates, times of TDM #1 and TDM #2
- IFX analytical methods including lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ)
- parameters for IFX modeling (IFX concentration, antibodies to IFX, status, albumin, concomitant use of methotrexate (MTX)

Pharmacokinetic (PK) Modeling:

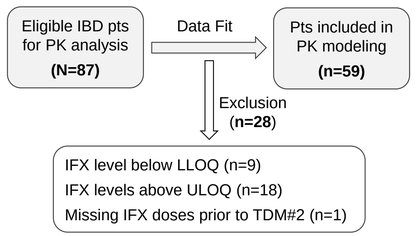
Two population PK models [2,3] were implemented in DoseMe® to fit individual patient data and determine PK parameter estimates using a single (TDM #1) or two IFX serum levels (TDM #1, TDM #2), respectively.

Model performances were evaluated using observed vs. model-predicted concentration plots, R^2, bias, mean absolute error (MAE) and root mean squared error (RMSE). Sensitivity defined as detection of sub-therapeutic IFX concentrations, specificity defined as identification of IFX pts with IFX ≥5 mg/mL, negative predictive value (NPV, IFX level >5 mg/mL), false positive rate and accuracy are provided for each model.

Statistical analysis:

Descriptive statistics (mean, median, interquartile range) were used to present values, frequencies and proportions.

Study Cohort



Results

Baseline Characteristics

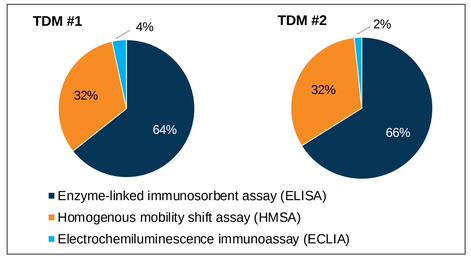
Table 1. Patient Characteristics

Variable (n=59)	Median or N	Min, Max
Age (years)	43	19, 76
Gender, male, n (%)	28 (47)	
Weight (kg)	77	47, 118.4
Disease type, n (%)		
Crohn's disease	40 (68)	
Ulcerative colitis	19 (32)	

Table 2. IFX Treatment Regimen

Variable	Median or N	Interquartile Range	Min, Max
IFX dose (mg/kg)	5.5	5.2 - 6.3	4.5, 12.0
Frequency (wk)	7.9	5.9 - 8.0	1.3, 9.7
IFX dose (mg/kg/wk)	0.75	0.6 - 1.3	0.5, 8.1
Frequency >q8wk, n (%)	12 (20)		
Length of IFX therapy (yrs)	1.3	0.7 - 4.3	0.2, 9.5

Figure 1. IFX Analytical Methods



- For ELISA and ECLIA, the LLOQ and ULOQ were 0.4 and 30 mg/ mL, respectively. For HMSA, the LLOQ and ULOQ were 0.98 and 34 mg/mL, respectively
- Median time between TDM #1 and #2 was 222 days (range, 11 to 2141 days)
- For TDM #1, 48 pts (81%) had trough and 11 pts (19%) had random IFX levels drawn, respectively

Table 3. Parameters Utilized for IFX Modeling

Parameter	TDM #1	TDM #2
IFX serum level (µg/mL)		
Median (interquartile range)	3.8 (1.9-10.9)	8.0 (4.0-11.1)
Antibodies to IFX status		
No. of pts positive	3 (5%)	2 (3.4%)
Albumin (g/dL)		
No. of pts w/ available level	43 (73%)	38 (64%)
Median (interquartile range)	4.2 (3.9-4.5)	4.1 (3.8-4.3)
Concomitant MTX use		
No. of pts	1 (1.7%)	3 (5%)

Pharmacokinetic Analysis

One-Compartment Model (Ternant D et al.)[2]

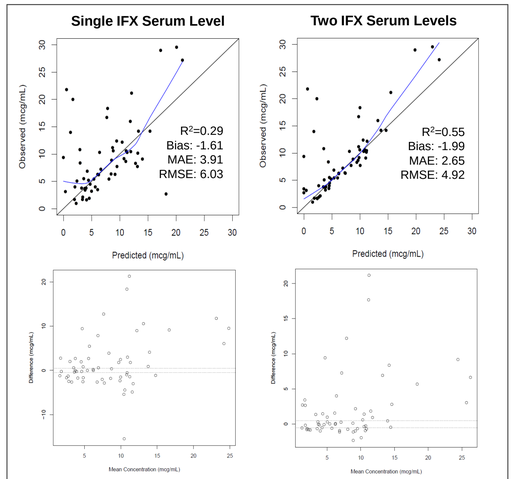


Figure 2. (*Top*) Observed *vs.* predicted IFX concentration plots using a single (*left*) and two IFX serum levels (*right*). Blue lines show best-fit model predictions. Corresponding Bland Altman plots representing fluctuations around limits of agreement (*below*).

Single IFX Serum Level Covariates: age, gender, weight

- Sensitivity: 82.4%
- Specificity: 71.4%
- Negative predictive value (NPV): 90.9%
- False positive rate: 28.6%
- Accuracy: 74.6%

Table 4. PK Parameters for One-Compartment Model

Cohort	No. Pts	V_D - L (CV%)	CL - L/day (CV%)
Ternant et al.[2] (IBD pts, no MTX)	143	6.80 (0.20)	0.37 (0.32)
Study pts (fitted, single IFX level)	59	7.18 (0.09)	0.45 (0.96)
Study pts (fitted, TDM #1/TDM #2)	59	7.19 (0.08)	0.55 (1.26)

- V_D was comparable for study pts with single IFX level (7.18 L *vs.* 6.80 L)
- CL indicated a higher difference (0.45 L/day *vs.* 0.37 L/day) with substantially more variance (CV%) present in the study cohort (0.96 *vs.* 0.32)

Two-Compartment Model (Fasanmade AA et al.)[3]

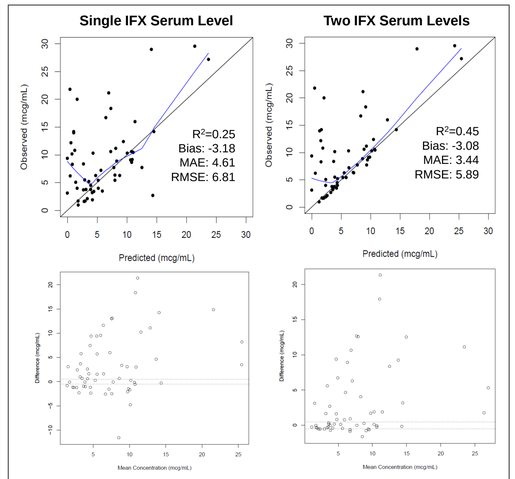


Figure 3. (*Top*) Observed *vs.* predicted IFX concentration plots using a single (*left*) and two IFX serum levels (*right*). Blue lines show best-fit model predictions. Corresponding Bland Altman plots representing fluctuations around limits of agreement (*below*).

Single IFX Serum Level Covariates: age, gender, weight, albumin level, antibodies to IFX status, concomitant use of MTX

- Sensitivity: 82.4%
- Specificity: 59.5%
- Negative predictive value (NPV): 89.3%
- False positive rate: 40.5%
- Accuracy: 66.1%

Table 5. PK Parameters for Two-Compartment Model

Cohort	No. Pts	V_D - L (CV%)	CL - L/day (CV%)
Fasanmade et al.[3] (UC pts)	482	3.63 (0.31)	0.37 (0.25)
Study pts (fitted, single IFX level)	59	4.97 (0.80)	0.50 (0.87)
Study pts (fitted, TDM #1/TDM #2)	59	4.98 (0.80)	0.49 (0.83)

- V_D was higher for study pts compared to published data (4.97 L *vs.* 3.63 L)
- CL was higher compared to published data (0.50 *vs.* 0.37 L/day) with substantially more variance (CV%) present in the study cohort (0.87 *vs.* 0.25)

- Decreased accuracy in lower concentration regions of plots is evident as shown by blue lines of best fit. This decreased accuracy tends to be due to underprediction with the majority of these pts achieving therapeutic IFX levels
- NPV for the one-compartment model was higher (90.9%) compared to NPV for the two-compartment model (89.3%), indicating higher certainty if a pt will achieve therapeutic IFX serum levels
- Sensitivities were comparable between both models. Specificity was higher for the one-compartment model (82.4%) compared to the two-compartment model (71.4%)

Discussion

This study evaluated the performance of Bayesian modeling for real-world IFX dose optimization using one and two-compartment models for comparison.[2,3]

- 59 pts (40 CD, 19 UC) with a median length of 1.3 years on IFX maintenance therapy were included in PK analyses.
- The one-compartment model[2] using a single IFX serum level and 3 covariates (age, gender, weight) allows prediction with 90.9% certainty (R^2=0.29), if a patient will achieve therapeutic IFX concentrations (≥5 mg/mL).
- The two-compartment model[3] using a single IFX serum level and 6 covariates (age, gender, weight, albumin, antibodies to IFX, use of MTX) allows prediction with 89.3% certainty (R^2=0.25), if a patient will achieve therapeutic IFX concentrations.
- PK modeling included both trough and random IFX serum levels.
- These data suggest there is no advantage on model fit nor predictive performance gained using a more complex two-compartment model compared to a simpler one-compartment model including a single trough or random IFX serum level.
- Multiple analytical methods with different sensitivities were used to assess serum concentrations and antibodies to IFX in this real-world study cohort, potentially contributing to observed variability in quantification.
- Limitations to this study include a small sample size of pts with IFX antibodies and with concomitant use of MTX for conclusive assessment. In addition, the median time between 2 TDMs was relatively long.

Conclusions

The one-compartment model using a single IFX trough or random serum level and 3 covariates can identify IBD pts with high predictability (91%), who will achieve therapeutic IFX drug concentrations (≥5 µg/mL).

Validation of this Bayesian forecasting model using a larger dataset would provide a decision tool for early identification of pts requiring IFX dose optimization.

Long-term application and study of pharmacokinetic TDM may also show improved IFX clinical response and reduced formation of IFX antibodies.

References

1. Frymoyer A. et al. JPGN 65: 639-45, 2017
2. Ternant D. et al. Clin Pharmacokinet 57: 1173-84, 2018
3. Fasanmade AA. et al. Eur J Clin Pharmacol 65: 1211-28, 2009