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A multi-model averaging approach improves the performance of model-guided infliximab de-escalation in patients with inflammatory bowel diseases

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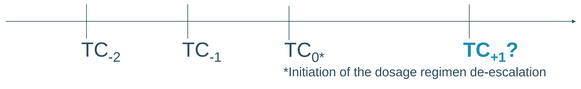
OBJECTIVES

- **Underexposure to infliximab** is a common cause of **loss of response** in patients with inflammatory bowel diseases.
- **Dosage regimen escalations** (higher dose and/or dosing frequency) are widely practised to boost infliximab trough concentrations and restore the response.
- **Long-term** maintenance of the **escalated dosage regimen** has financial, practical, and potentially safety implications.
- **Dosage regimen de-escalation** could put patients at **risk for underexposure** and trigger again **loss of response**.
- **To ensure adequate** – but **not unnecessarily high – exposure**, we aimed to identify the best population pharmacokinetic model or a combination of models for guiding infliximab de-escalation.

METHODS

- Data of **54** patients (from a retrospective, single-centre cohort study) who underwent infliximab dosage regimen de-escalation after an earlier escalation, including covariate and trough concentration (TC) data.
- One to three consecutive infliximab TCs (TC_{-2}, TC_{-1}, TC_0) before initiation of the dosage regimen de-escalation were used in addition to covariate data to **predict the next infliximab TC (TC_{+1})**.



- NONMEM (version 7.5; Icon plc) was used for Bayesian forecasting.

Single-model approach

- **15** published infliximab population pharmacokinetic models

(Aubourg_2015, Brandse_2016 Brandse_2017, Buurman_2015, Dotan_2014, Dreesen_2019, Dreesen_2020, Fasanmade_2009, Fasanmade_2011, Grišić_2021, Passot_2016, Petitcollin_2019, Ternant_2008, Ternant_2014, Ternant_2018)

Multi-model approaches

- a model selection algorithm (MSA) and a model averaging algorithm (MAA)[1]
- using the 15 models jointly
- weighting scheme based on the squared prediction errors[1]

Compare **predictive performance metrics**

Accuracy: relative bias (rBias)

- between ±20% with a 95% CI including zero considered clinically acceptable

$$\text{rBias} = \frac{1}{n} \times \sum_1^i \left(\frac{(\text{predicted}_i - \text{true}_i)}{\text{true}_i} \right) \times 100\%$$

Precision: relative root mean square error (rRMSE)

- as low as possible with no pre-specified threshold

$$\text{rRMSE} = \sqrt{\frac{1}{n} \times \sum_1^i \left(\frac{(\text{predicted}_i - \text{true}_i)^2}{\text{true}_i^2} \right)} \times 100\%$$

RESULTS

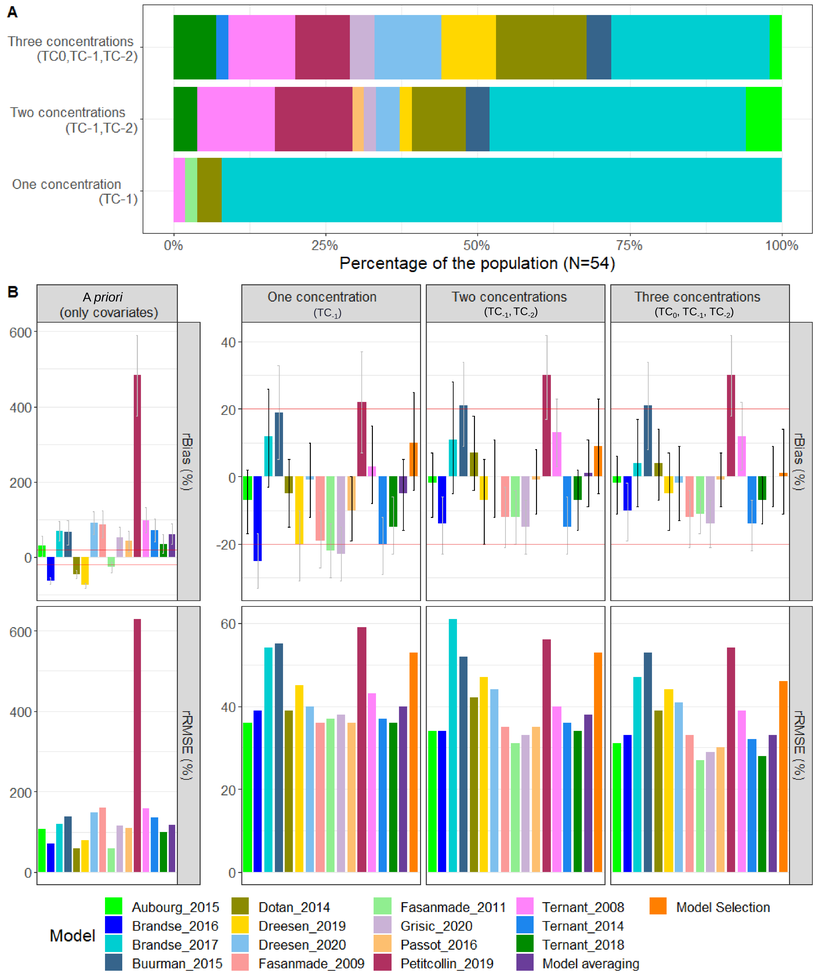


Figure 1. (A) Proportion of model with the highest weight in the study population (n=54) in the three Bayesian forecasting settings. **(B)** The predictive performance of single model approaches and multi-model approaches for predicting the TC_{+1} in various settings: A *priori* prediction (only covariates); Bayesian forecasting using one (TC_{-1}), two (TC_{-1},TC_{-2}), and three (TC_0, TC_{-1}, TC_{-2}) infliximab concentrations. Whiskers cover the 95% CI of the relative bias calculated via the standard error (black whisker indicated 95% CI including 0).

- The Brandse_2017 model had the highest weight in most patients, irrespective of the number of TCs considered (50/54 [93%] of patients when using TC_{-1} only; 14/54 [26%] of the patients when using all three TCs).
- Having the highest weight in most patients (which indicates the best fit to the available TCs) did not make the Brandse_2017 model the least biased in the single-model prediction approach.
- Covariate-based (a *priori*) predictions with any model was clinically unacceptable (rBias -75% to +483%, rRMSE 58% to 629%).
- The predictive performances of all models greatly improved by considering at least one infliximab TC (Bayesian forecasting; TC_{-1}: rBias -25% to +22%, rRMSE 36% to 59%).
- Using additional previous TCs improved the predictions only marginally (TC_{-1} and TC_{-2}: rBias -15% to +30%, rRMSE 31% to 61%; TC_0, TC_{-1}, and TC_{-2}: rBias -14% to +30%, rRMSE 27% to 54%).
- Five out of fifteen models (Aubourg_2015, Brandse_2017, Dotan_2014, Dreesen_2020, Passot_2016) displayed clinically acceptable bias when using one to three TCs (rBias -10% to +12%).
- Both MAA and MSA resulted in clinically acceptable predictions, with rBias -5% and +10%, respectively, when considering TC_{-1} and rBias 0% and +1% when considering all three TCs.
- MAA performed systematically better than MSA, not only in terms of accuracy but also in terms of precision.
- Performance of the MAA was less sensitive to the number of TCs considered in Bayesian forecasting, while the predictive performance of the MSA and single-model approaches improved with the number of samples considered.

CONCLUSIONS

- The Brandse_2017 model displayed the highest weight in the multi-model approaches.
- The multi-model approaches, especially MAA, provided a more reliable Bayesian forecast compared to the single-model approach for guiding infliximab de-escalation in patients with inflammatory bowel diseases.

REFERENCES

[1] D. W. Uster et al. CPT (2021) 109, 175–18

CONTACT INFORMATION

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