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Pharmacokinetic Model-Informed Precision Dosing of Natalizumab in Multiple Sclerosis

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ABSTRACT

Intravenous natalizumab is an effective treatment for relapsing–remitting multiple sclerosis. However, the standard treatment interval of 4 weeks may be excessive for many patients. Personalized interval extension using therapeutic drug monitoring (TDM) can result in adequate drug exposure while reducing hospital visits and healthcare costs. Here, we investigate to which extent TDM-guided personalized dosing can benefit from model-informed precision dosing (MIPD). Individual posterior PK estimates were derived using patient weight and two trough concentrations at the standard dose interval by Bayesian estimation using a newly developed population PK model. MIPD was compared to a previously deployed TDM-guided stratified personalized dosing protocol (SPD) using a decision tree to personalize dosing intervals. Accuracy (mean prediction error) of the predicted dosing intervals was 4.8% versus 24% for model-informed estimates versus decision tree, respectively, when aiming for a 10 μg/mL trough concentration, and 4.8% versus 86% when aiming for 5 μg/mL. Corresponding precision (root mean square error) was 2.3 versus 4.0, and 1.5 versus 5 μg/mL. Finally, we evaluated the feasibility of a MIPD approach to attain a therapeutic trough of 2 μg/mL. Simulating MIPD showed a reduction in the average infusions versus the standard interval by 40%, with an average dose interval of 7 weeks, while maintaining adequate drug exposure. MIPD was concluded to be superior to the conventional TDM-guided personalized dosing approach in terms of enhanced precision in individual dose interval selection, enabling more efficient interval extensions. Simulations supported the clinical deployment of natalizumab MIPD.

1 | Introduction

Treatment with intravenous (i.v.) natalizumab is highly effective for patients with relapsing–remitting multiple sclerosis (RRMS) [1]. Natalizumab is an IgG4κ therapeutic monoclonal antibody (mAb) targeting the α4β1 integrins on lymphocytes. Blocking α4β1 abolishes the lymphocytes ability to bind to vascular cell adhesion molecules, which in turn prevents entry to the central nervous system through the endothelium [2, 3]. However, prolonged natalizumab treatment increases

Summary

- What is the current knowledge on the topic?
  - Natalizumab is an effective treatment for multiple sclerosis. However, the uniform dosing approach of natalizumab is excessive for most patients. Extended interval dosing has been shown to maintain sufficient drug exposure and efficacy. Therapeutic drug monitoring (TDM) allows personalized interval dosing.
- What question did this study address?
  - We developed a population pharmacokinetic model to simulate model-informed precision dosing (MIPD) of patients treated with natalizumab. This study evaluated whether personalized interval dosing can be further improved by MIPD compared to a previously conducted pragmatic TDM-guided dose extension protocol.
- What does this study add to our knowledge?
  - MIPD enables accurate and precise target attainment in personalized dosing protocols. MIPD allows for further interval extension while retaining minimal trough levels of 2 μg/mL.
- How might this change clinical pharmacology or translational science?
  - MIPD-based personalized dosing can be preferential in terms of healthcare costs and patient burden rather than a one-size-fits-all approach.

the risk of progressive multifocal leukoencephalopathy (PML) due to a compromised immunosurveillance in the central nervous system [4].

A large retrospective cohort study demonstrated a reduction of PML risk with extended treatment intervals versus the approved 4-week interval [5]. Meanwhile, multiple retrospective studies indicated that natalizumab efficacy is not compromised with reduced exposure [6, 7]. Recent studies evaluated the extension of the natalizumab dosing interval prospectively. Within a randomized controlled (NOVA) trial, patients assigned to either 4- or 6-week intervals displayed high efficacy [8]. Extended interval dosing guided by therapeutic drug monitoring (TDM) led to treatment intervals ranging from 5 to 7 weeks [9]. Tailoring treatment based on drug concentrations is a more practical approach than the measurement of α4-integrin saturation, which necessitates the isolation of peripheral blood mononuclear cells. A natalizumab concentration in serum of 1–2 μg/mL was proposed as a safe and effective TDM trough target, as this would saturate approximately 50% of targets [10, 11]. Saturation levels dropping below 20%–40% due to cessation of natalizumab treatment correlated with the return of disease activity [12]. Individual tailoring of the natalizumab dosing regimen can decrease treatment burden, improve cost-effectiveness, and reduce the risk of infections by opportunistic viruses [10].

A recent study (NEXT-MS) evaluated TDM-guided interventions that were performed on a decision tree, followed by a stepwise iteration process, hereinafter referred to as the stratified personalized dosing (SPD) protocol [13]. A more sophisticated approach would utilize model-informed precision dosing (MIPD). MIPD leverages covariate information, observed drug concentrations, and prior knowledge of population pharmacokinetic (PK) parameters to predict individual drug concentrations, facilitating dose adjustments [14]. Therapeutic antibodies may be suitable for such an approach, as they exhibit large interindividual variability (IIV), and in the case of natalizumab, low inter-occasion variability [15]. As an example, implementation of MIPD for infliximab in inflammatory bowel disease improved the attainment of the therapeutic target [16]. A prospective trial with MIPD of infliximab resulted in the reduction of the loss of response compared to conventional dosing [17].

Here we evaluated the performance and benefits of MIPD for personalized natalizumab dosing utilizing a newly developed population PK model. The analysis was conducted based on the SPD data, with individuals targeting trough concentrations of 10 and 5 μg/mL. The aim was to compare target attainment of predicted trough levels between the SPD and MIPD approaches. Retrospectively, we assessed the target attainment of observed trough levels by both methods. Furthermore, we evaluated the model's performance in predicting trough levels at extended dosing intervals.

Furthermore, simulations of MIPD aiming at a pharmacokinetic trough target of 2 μg/mL were explored and assessed on (I) target attainment, in terms of the period during which concentrations are below the target before administering the next infusion, and (II) quantification of drug savings based on dosing frequency versus standard interval dosing.

2 | Methods

2.1 | Participants and PK Data MS Studies

Clinical data were pooled from three clinical studies of RRMS patients treated with natalizumab. Natalizumab doses were administered intravenously to patients at a dose of 300 mg. All patients in the STDMS [15] study were on the standard approved dose interval of 4 weeks. The PDNMS [9] and NEXTMS [13] studies were both prospective multicenter trials, with patients on at least 6 months of natalizumab treatment switching to personalized extended intervals. Individuals who exhibited anti-drug antibodies were excluded. Natalizumab trough levels were measured by sampling 5 mL of blood through the intravenous drip prior to the next infusion.

2.2 | Stratified Personalized Dosing

SPD in the NEXTMS study was guided by a decision tree informed by two trough concentrations of the standard 4 weekly dose interval. The study included two cohorts, with the main and low groups targeting concentrations of 10 μg/mL and 5 μg/mL, respectively. For instance, if a patient had two measurements above 45 μg/mL in the main cohort, the dose interval was adjusted to 7 weeks. Patients were monitored, and trough concentrations were measured at an extended interval. For each SPD-informed extended interval, one observation per

patient was randomly selected. For more details, see Supporting Information, Section 1.

2.3 | Natalizumab Concentration Assay

Serum levels of natalizumab were measured at the Sanquin Laboratory Amsterdam with a crosslinking ELISA, with polyclonal rabbit anti-natalizumab F(ab')2 fragments for capture and chimeric anti-IgG4-HRP monoclonal antibodies for detection, with a capture concentration of 0.125 μg/mL [18]. The lower limit of quantification (LLOQ) was 0.025 μg/mL, and the upper limit of quantification (ULOQ) was 3277 μg/mL. The coefficient of variation (CV%) of intra-assay and interassay precisions was 1.1%–5% and 0.6%–3%, respectively.

2.4 | Population PK Model Development

A population PK model for natalizumab was developed using pooled data from patients in the maintenance phase. The model fitting utilized the FOCE+I method. Various structural models, including one- and two-compartment models with linear and nonlinear elimination routes, were tested. Nonlinear elimination models explored included target-mediated drug disposition models and Michaelis–Menten approximation. Model selection was based on the objective function value (OFV) and goodness-of-fit plots. Interindividual variability was modeled exponentially. Residual variability was evaluated with proportional and combined additive-proportional error models during early PK development. Allometric scaling was applied to clearance and central volume based on weight, using a reference value of 70 kg and an estimated scaling exponent. The final model was evaluated by nonparametric bootstrapping and prediction-corrected visual predictive checks [19]. Further details can be found in the Supporting Information, Section 2.

2.5 | In Silico Evaluation of Model Informed Precision Dosing

The constructed PK model was implemented for precision dosing using cross-validation to assess the performance of MIPD on an independent dataset [20]. The dataset was randomly split into 5 roughly equal groups of individuals. The training set consists of four of five groups to estimate the population PK parameters. Subsequently, the estimated PK model was fit to individuals of the remaining validation group, computing individual Bayesian posterior PK estimates ("MAXEVAL = 0" option), often referred to as empirical Bayes estimates (EBEs). Individual characteristics for computation were baseline weight and two trough samples at the standard treatment interval of 4 weeks. Individual PK parameters were used throughout the study for MIPD, enabling the projection of concentration–time profiles, trough levels, and selection of personalized intervals. This method of training, fitting, and applying MIPD was conducted for each of the fivefolds, depicted in Figure 1. A k-fold of 5 is a common choice as smaller k values result in higher variability of parameter estimates and are computationally less demanding [21]. Individuals were selected only if they had at least one trough sample at a personalized interval (e.g., 5 or more weeks).

MIPD was compared to the previously applied SPD protocol (Figure 1). Individual PK parameters were utilized to predict trough levels across a range of intervals, including the SPD interval (Δt_{SPD}). The Δt_{MIPD} was calculated as the interval with the shortest distance between log-transformed trough prediction and trough target. Target attainment was calculated for the predicted trough levels at Δt_{SPD} and Δt_{MIPD}. The mean percentage error (MPE) and root mean squared error (RMSE) were calculated to determine accuracy and precision, respectively. Equations can be found in the Supporting Information, Section 3. Additionally, CV% of predicted trough concentrations was calculated to assess precision.

Patients in the SPD study were not always dosed with the model-informed interval; thus, a retrospective assessment was carried out on the trough concentrations by stratifying them on the (mis)match, $\Delta t_{MIPD} - \Delta t_{SPD}$, in weeks. Three scenarios arise: (I) where the model-selected dose interval corresponds to the SPD protocol; (II) where the model predicts a further extension; or (III) a reduction of the interval. A single observed trough level was randomly selected per patient.

2.6 | Model Performance on Predicted Personalized Interval Trough Samples

The predictive performance of a model was evaluated based on the prediction error and absolute prediction error. Accuracy was assessed by the mean percentage prediction error (MPPE) and precision by the mean absolute prediction error (MAPE) and root mean squared error (RMSE).

The logarithmic prediction-to-observation ratio was calculated to find the mean, and the according normal distribution, which was suggested to be superior to other relative prediction errors in case of heteroscedasticity [22].

2.7 | MIPD Simulation Strategy

A simulation of MIPD was conducted to assess whether the patients in our dataset can reach lower trough levels using four algorithms in ascending order of risk. We used the same SPD dataset, including all individuals in the NEXTMS trial who had two standard interval trough samples. The population PK model applied was the conclusive model derived through cross-validation. Individual PK parameters were used to predict trough samples for a range of dose intervals, limited to complete weeks. The personalized interval was chosen based on the algorithm, taking into account the distance between the log-transformed individual trough prediction and the therapeutic trough target. Algorithms are shown below, with A1 and A3 being limit constrained, such that only dose intervals were selected which resulted in trough levels above the target.

A1 Trough target of 5 μg/mL, limit constrained at 5 μg/mL.

A2 Trough target of 5 μg/mL.

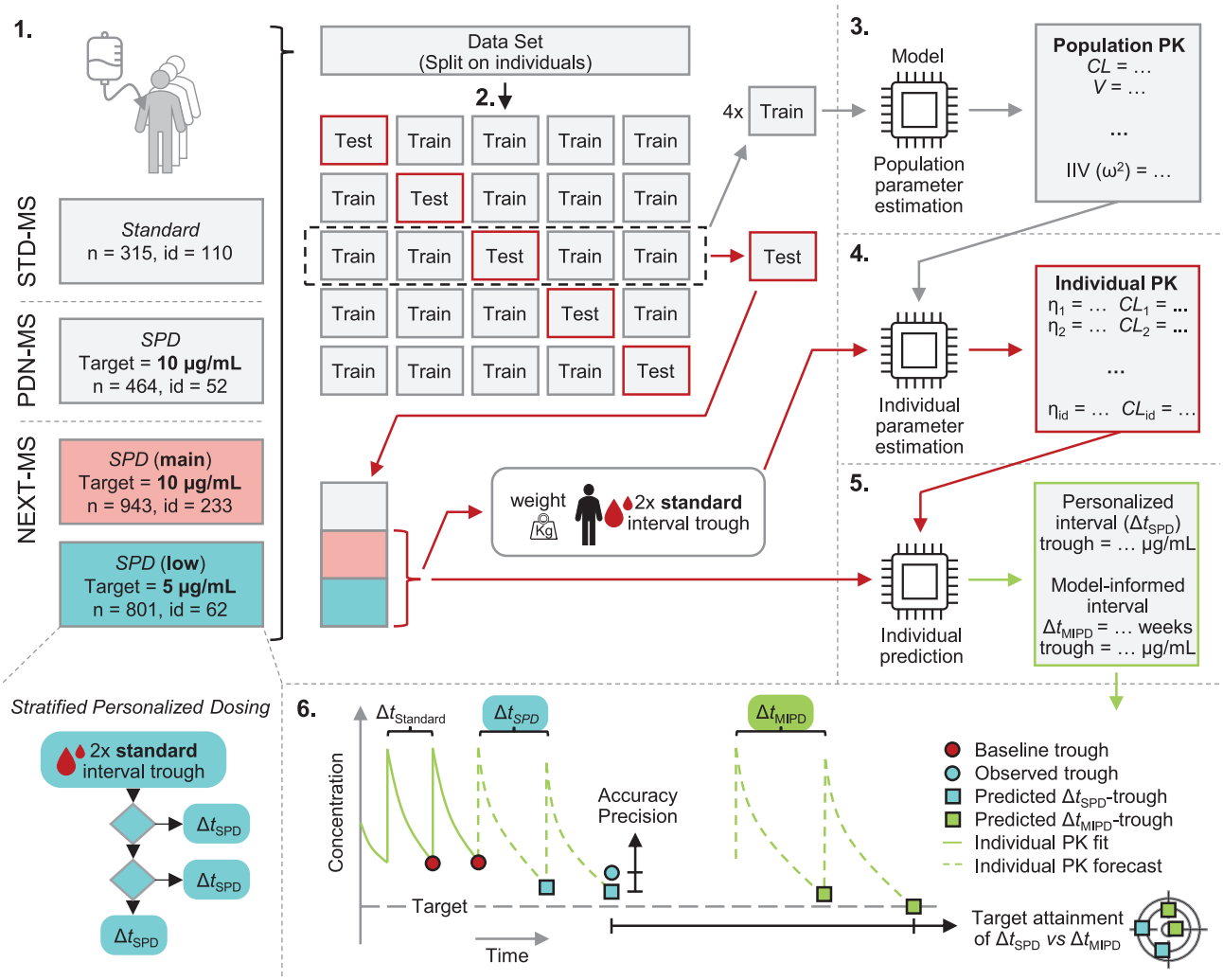

FIGURE 1 | Cross-fold validation overview and illustration of personalized interval dosing by either the *stratified personalized dosing* (SPD) or *model-informed precision dosing* (MIPD) protocol. (1) Datasets of three studies were combined, in which personalized intervals (Δt_{SPD}) were selected using a decision tree based on two standard interval trough levels. (2) The following section was repeated five times; the dataset was split into five subsets, four folds combined as the training set and the remaining fold as the test set. (3) The training set was used for population pharmacokinetic (PK) parameter estimation. (4) The test set was used for validation purposes. Data of individuals with weight and two troughs were used for Bayesian estimation of individual PK parameters. (5) Using the individual PK model, trough levels were predicted for multiple intervals, which were then applied to determine the model-informed interval (Δt_{MIPD}). (6) Time–concentration profile switching from standard interval to Δt_{SPD} or Δt_{MIPD}. Visualization of the comparison between SPD and MIPD on target attainment, and model performance calculated on observed and predicted trough levels. *n* = samples, id = individuals, CL = clearance, V = volume, η = individual-specific deviation from the population mean.

A3 Trough target of 2 µg/mL, limit constrained at 2 µg/mL.

A4 Trough target of 2 µg/mL.

To assess the actual distribution of observations following the execution of an algorithm, prediction errors were utilized. The expected error, randomly sampled from the Ln Q error distribution determined in the model performance section, was multiplied by the prediction to yield simulated observations at trough. The risk of reduced efficacy was denoted as the duration in consecutive days an individual had natalizumab concentrations below a threshold, either 2 or 1 µg/mL. We calculate the duration during which the model predicts concentrations below 2 or 1 µg/mL, using the model-informed interval and individual PK estimates to reach the simulated trough observations. Furthermore, the benefits of disease burden and drug savings were expressed as the means of infusions per person per year.

2.8 | Software

Data management, analysis, and visualization of NONMEM results were done in R (Version 4.2.1) using Rstudio (Version 1.1.456). Pharmacokinetic and regression models were performed with the nonlinear mixed-effects modeling software package NONMEM (Version 7.5.0). Models were executed using Perl Speaks Nonmem (PSN, Version 5.3.0) with Pirana (Version 21.11.1) or by the R package RspeaksNONMEM (https://github.com/MikeKSmith/rspeaksnonmem). The NONMEM code is provided in the Supporting Information.

3 | Results

3.1 | Participant Characteristics at Baseline

Serum PK samples of RRMS patients in the maintenance phase of intravenously administered natalizumab were acquired (Figure S1). After exclusion, the dataset for PK model development comprised 2523 observations (2489 at trough, 34 at peak) from 379 RRMS patients across 20 clinics in the Netherlands, with baseline characteristics outlined in Table 1 (Table S1 and Figure S2). Weight, age, and height were normally distributed, with a female-to-male ratio of 4 to 1. The median serum concentration observed across the entire dataset was 13 μg/mL (range 0.025–130 μg/mL; IQR 8.4–21), and the median dose interval was 35 days (range 21–64 days; IQR 28–42).

TABLE 1 | Patient baseline characteristics ($n = 379$ patients).

Weight, kg	73 (64–83)
Height, cm	174 (168–180)
Age, years	38 (32–47)
Sex	
Female, *n* (%)	298 (78.6%)
Male, *n* (%)	81 (21.4%)

Note: Values are presented as median (Interquartile range) or n = count (frequency %).

3.2 | Two-Compartment PK Model

PK of i.v. natalizumab was best described with a two-compartment PK model containing both linear (first-order) and nonlinear target-mediated elimination following Michaelis–Menten kinetics (Tables 2, S2, Section 4, Figure S3A). Selection of the proportional error model was based on its better accuracy at lower concentrations and its appropriate reflection of the error across the entire range of the natalizumab ELISA assay. Precision of parameters was estimated with RSEs on fixed effects < 50% and random effects < 50%, except for the covariate effect of weight on central volume (70.4%) (Table S4). Effect sizes were calculated as the change in the PK parameter at the covariate values at the 2.5th and 97.5th percentile compared to their reference values. The effect sizes for weight on clearance and central volume were, respectively, 0.85–1.34 and 0.93–1.14 (Figure S3B,C). The final model compared to another natalizumab population PK model showed a similar clearance (0.164 vs. 0.15 L/h), similar central volume (3.48 vs. 3.76 L), and a substantially higher peripheral volume (3.48 vs. 1.82 L) [23].

Goodness-of-fit plots indicated no structural biases toward the time of sampling, the time after dose, or the observations, and adequately recapitulated the observed data (Figure S4). A

TABLE 2 | Population pharmacokinetic model parameter estimates.

	Final model	Cross-validation model	Bootstrap final model ($N = 500$)
Parameter	**Mean (%RSE)**	**Mean**	**Mean (95% CI)**
Clearance (CL, L/d)	0.164 (2.5)	0.165	0.164 (0.155, 0.173)
Central Volume of distribution (Vc, L)	3.48 (4)	3.5	3.49 (3.25, 3.76)
Peripheral Volume of distribution (Vp, L)	3.48 (12.4)	3.46	3.47 (2.98, 3.95)
Intercompartmental clearance (Q, L/d)	0.4 (Fixed)	0.4 (Fixed)	0.4 (Fixed)
Maximum elimination rate (Vmax, mg/d)	2.86 (7.7)	2.84	2.85 (2.52, 3.20)
Concentration at half Vmax (Km, mg/L)	0.875 (12.7)	0.85	0.84 (0.11, 1.55)
Θ_{WTCL} (WT on CL)	0.6 (16.6)	0.59	0.60 (0.44, 0.76)
Θ_{WTCL} (WT on Vc)	0.26 (70.4)	0.25	0.25 (0.01, 0.48)
IIV (CV%)			
CL	22.8 (16.6)	22.9	22.7 (19.4, 25.7)
Vp	31.5 (49.5)	32.8	30.3 (1.96, 43.2)
Vmax	26 (23.1)	26.0	26.1 (20.7, 31.4)
Residual (CV%)			
Proportional error	22 (2.8)	21.9	21.9 (21.0, 22.9)

Note: $CL_i = CL_{pop} \times (\text{Weight}/70)^{\theta,WTCL}$, $Vc_i = Vc_{pop} \times (\text{Weight}/70)^{\theta,WTVC}$. Shrinkage in the final model on CL, Vp, Vmax was 15.4%, 66.7%, 35%, respectively. Intercompartmental clearance was fixed to 0.4 L/day as estimated in a previous natalizumab PK model [23]. The parameters of the 5-fold cross-validation were the result from the mean parameter estimated on the training set for all five iterations. All 500 bootstrap runs converged successfully. The results were reported as the mean along with the 95% confidence interval (95% CI), calculated using the 2.5th and 97.5th percentiles of the parameter distributions. Abbreviations: CV%, coefficient of variation; IIV, interindividual variability; RSE, relative standard error; Θ_{WTCL}, the covariate effect of weight on clearance; Θ_{WTVC}, the covariate effect of weight on the central volume of distribution.

nonparametric bootstrap evaluation of the final PopPK model was performed, showing that all 500 bootstrap runs converged successfully (Table 2). A visual predictive check was evaluated and showed general agreement between observed data and simulated 95% confidence intervals (Figure S5).

3.3 | Improved Target Attainment of MIPD Versus SPD Protocol

Using the PK model, we set out to explore its potential use in guiding personalized dose intervals by MIPD compared to a previously conducted SPD protocol. We implemented cross-validation to evaluate MIPD of individuals who were not included in the PK model fitting process (Tables S5 and S6). To this end, individual PK estimates were used to determine model-informed dose intervals to reach either 10 or 5 μg/mL at trough for, respectively, 168 and 32 individuals. Median (IQR) intervals between the SPD and MIPD protocols were, respectively, 5 (5, 6) weeks and 6 (5, 6) weeks (Figure 2A,C). Considering the accuracy and precision of target attainment, trough concentrations were predicted for intervals selected either in the SPD protocol (Δt_{SPD}) or by using MIPD (Δt_{MIPD}). The mean percentage error was reduced for MIPD compared to SPD for both the main and low target concentration (respectively, 4.8 vs. 24.4% and 4.8 vs. 86.2%; Table 3). The root mean square error was reduced for MIPD compared to SPD for both the main and low target concentration (respectively, 2.31 vs. 3.95 μg/mL and 1.53 vs. 5.02 μg/mL; Table 3). Predicted trough levels, associated with Δt_{MIPD}, displayed smaller variability than those associated with Δt_{SPD} for both the main and low target concentration (respectively, 5.1 vs. 9.7 CV% and 2.3 vs. 6.8 CV%; Figure 2B,D).

Trough target attainment of MIPD was examined by grouping trough samples based on a match or mismatch of Δt_{MIPD} and Δt_{SPD} (Figure 2E). Overall, in the case of targeting 10 μg/mL at trough, 65% of the samples had a match, and these had a median trough concentration of 12 (IQR 9.4–13.7) μg/mL, whereas for 31% of the samples, the model-informed interval was 1 week longer (mismatch = 1; concentration 15.5 [12–18] μg/mL), and for 3%, the model-informed interval was 1 week shorter (mismatch = −1; concentration of 5.2 (2.4–7.4) μg/mL).

For the treatment arm targeting 5 μg/mL, 28% of cases were in agreement between Δt_{MIPD} and Δt_{SPD} resulting in a median (IQR) of 6.4 (3.7–7.7) μg/mL (Figure 2F). During the study, trough concentrations were monitored after the extension of the dose interval, and participants were further extended if trough concentrations persisted above 10 μg/mL. This resulted in trough samples at the model-informed interval for 13 of 22 participants, which improved target attainment compared to the initial SPD interval (Figure 2G). Ten participants did not have data at the

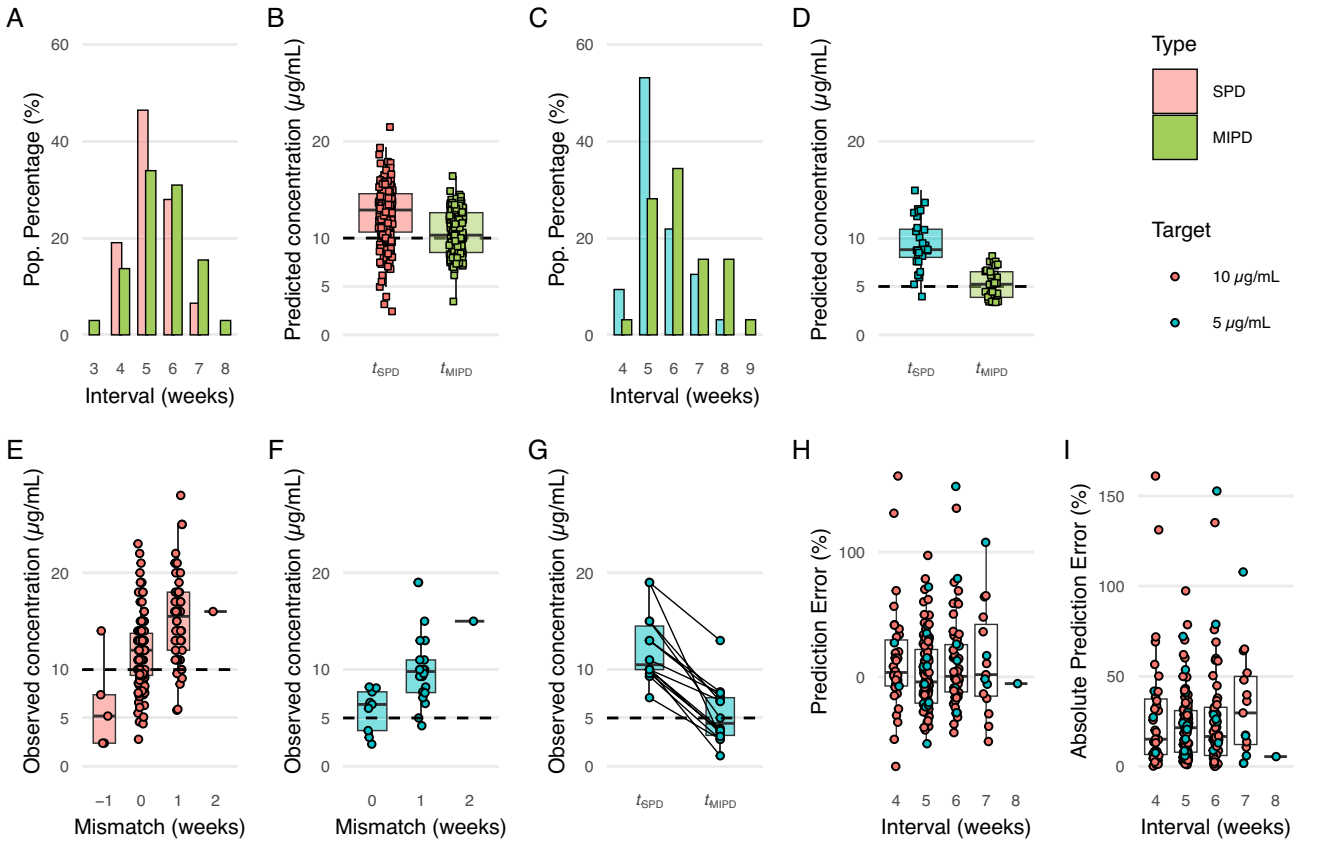

FIGURE 2 | MIPD versus SPD protocol. Distribution of personalized intervals, either as selected by the SPD protocol (Δt_{SPD}) or model (Δt_{MIPD}), for (A) 10 μg/mL and (C) 5 μg/mL. Boxplot of predicted concentrations associated with Δt_{SPD} or Δt_{MIPD} for (B) 10 μg/mL and (D) 5 μg/mL. Observed concentrations stratified by the mismatch (= $\Delta t_{MIPD} - \Delta t_{SPD}$) in weeks for (E) 10 μg/mL and (F) 5 μg/mL. (G) Observed concentrations after further extension from the initial SPD interval, resulting in the interval as proposed by the model. (H) Distribution of prediction errors, stratified by interval. (I) Distribution of absolute prediction errors, stratified by interval.

TABLE 3 | Performance of target attainment.

Approach	Target (μg/mL)	MPE (%) [95% CI]	RMSE [95% CI]
SPD	10	24.4 [19.7; 29.1]	3.95 [3.3; 4.6]
MIPD	10	4.8 [1.37; 8.22]	2.31 [1.93; 2.68]
SPD	5	86.2 [68.1; 104]	5.02 [3.28; 6.76]
MIPD	5	4.81 [−5.81; 15.4]	1.53 [1; 2.06]

Note: Performance of target attainment using the error between trough target and trough concentration for a personalized interval. The personalized interval was informed by either a decision tree guided by therapeutic drug monitoring, referred to as stratified personalized dosing (SPD), or a model-informed precision dosing (MIPD) approach. Mean percentage error (MPE) for accuracy and root mean square error (RMSE) for precision.

initial SPD interval but only had observations at Δt_{MIPD}, resulting in a median (IQR) concentration of 5.7 (5.0–6.6) μg/mL (Data not shown).

Model-informed personalized interval dosing compared to the protocol would reduce the average number of infusions per person per year from 10.2 to 9.9 (reduction of 3%), and from 9.8 to 8.7 (reduction of 11%) for 10 and 5 μg/mL as therapeutic trough target, respectively.

The evaluation of model performance in predicting observed concentrations was conducted. Median prediction errors were close to zero for all dose intervals, with a mean percentage prediction error of 7.7%, proving no significant bias (Figure 3H). Additionally, to address precision, the root mean square error was computed and found to be 3.6 μg/mL. Absolute prediction errors stratified by interval were similar across all groups, with a mean absolute prediction error of 26% (Figure 3I). The final model parameters derived from this cross-validation procedure are shown in Table 1, displaying minimal disparity from the reduced model.

3.4 | Benefits and Risks When Lowering the Trough Target In Silico

The final model was employed for the simulation of four different increasingly aggressive MIPD algorithms to lower the therapeutic target, resulting in theoretical personalized intervals graphically represented in Figure 3A. Of these, algorithm 3 might represent the most optimal scenario. Algorithm 3 aims at trough levels of 2 μg/mL, while selecting only intervals with predicted trough concentrations above 2 μg/mL, resulting in dose intervals ranging from 4 to 10 weeks. Despite the limitation for the selection of trough levels above 2 μg/mL in algorithm 3, 11% of patients had expected observations at trough falling below 2 μg/mL (Figure 3B). However, only one of 222 individuals (less than 0.5%) would have 2 days below 1 μg/mL, potentially exposing them to insufficient drug (Figure 3C). Applying MIPD with algorithm 3 would reduce infusions compared to standard dosing by 39% to an average of eight infusions per person per year (Figure 3D). Algorithm 2, as used in the previous chapter, aimed to reach 5 μg/mL at trough, showing a 35% reduction. The more risk-intensive algorithm 4 would result in 6.25% of patients with natalizumab concentrations below 1 μg/mL for 1–5 days.

4 | Discussion

Here, we demonstrated the improvement of trough target attainment by MIPD of i.v. natalizumab versus a SPD-guided approach. We assessed MIPD of participants who had received at least 6 months of natalizumab treatment and did not exhibit antidrug antibodies. Although antidrug antibodies are frequent during the first months of treatment, they are largely transient in nature [24]. A new population PK model was built using the full dataset. Individual PK parameters for MIPD were based on the population PK model, the baseline weight, and informed by two trough samples at the standard 4-week interval. The assessment employed a cross-validation methodology, guaranteeing that MIPD was implemented on individuals excluded during the population parameter estimation, mimicking real-life application. Selection of the personalized dose interval with a model improved the precision and accuracy of target attainment. Specifically, MIPD did not exhibit a bias for overprediction, as observed in the SPD-guided approach. Furthermore, the imprecision in terms of the RMSE of MIPD compared to SPD for target concentrations of 10 and 5 μg/mL was reduced by 42% and 70%, respectively. The variability of trough levels for either 10 or 5 μg/mL as a target decreased by 47% and 66%, respectively. The intervals chosen in the SPD protocol that matched with the model exhibited concentrations closer to the desired trough level than those that mismatched, showing improved target attainment. The performance of the model to predict observed trough concentrations was assessed and revealed a mean absolute prediction error of 26% and a mean percentage prediction error of 7.7%. Furthermore, MIPD was demonstrated to enable further interval extensions while retaining sufficient target attainment with trough concentrations for most patients above 2 μg/mL. Simulations of MIPD indicated a 40% reduction in hospital visits for administration of natalizumab, supposedly leading to cost savings and alleviation of the treatment burden. In evaluating cost-effectiveness, it is essential to consider fewer hospital visits, lower drug consumption, the expenses of TDM, and the potential risks of subtherapeutic exposure and more. However, a pharmacoeconomic analysis is outside the scope of this study.

The selection of the initial personalized interval guided by SPD was informed by findings in a prior study of interval extension [9]. For instance, here it was observed that maintaining trough levels above 45 μg/mL at the 4-week interval allowed for a 7-week interval to achieve a target concentration of 10 μg/mL. However, a lower trough target was deemed possible, but no existing data addressed this specific scenario. Therefore, an exploratory arm was pursued in the study aiming at a trough target of 5 μg/mL. As a result, target attainment was worse for the group targeting 5 versus 10 μg/mL at trough, and MIPD proved to be more beneficial in improving target attainment in the former case.

Inclusion of target mediated drug disposition by nonlinear elimination significantly improved the natalizumab PK model. Physiologically, this might correspond to either α4-integrin

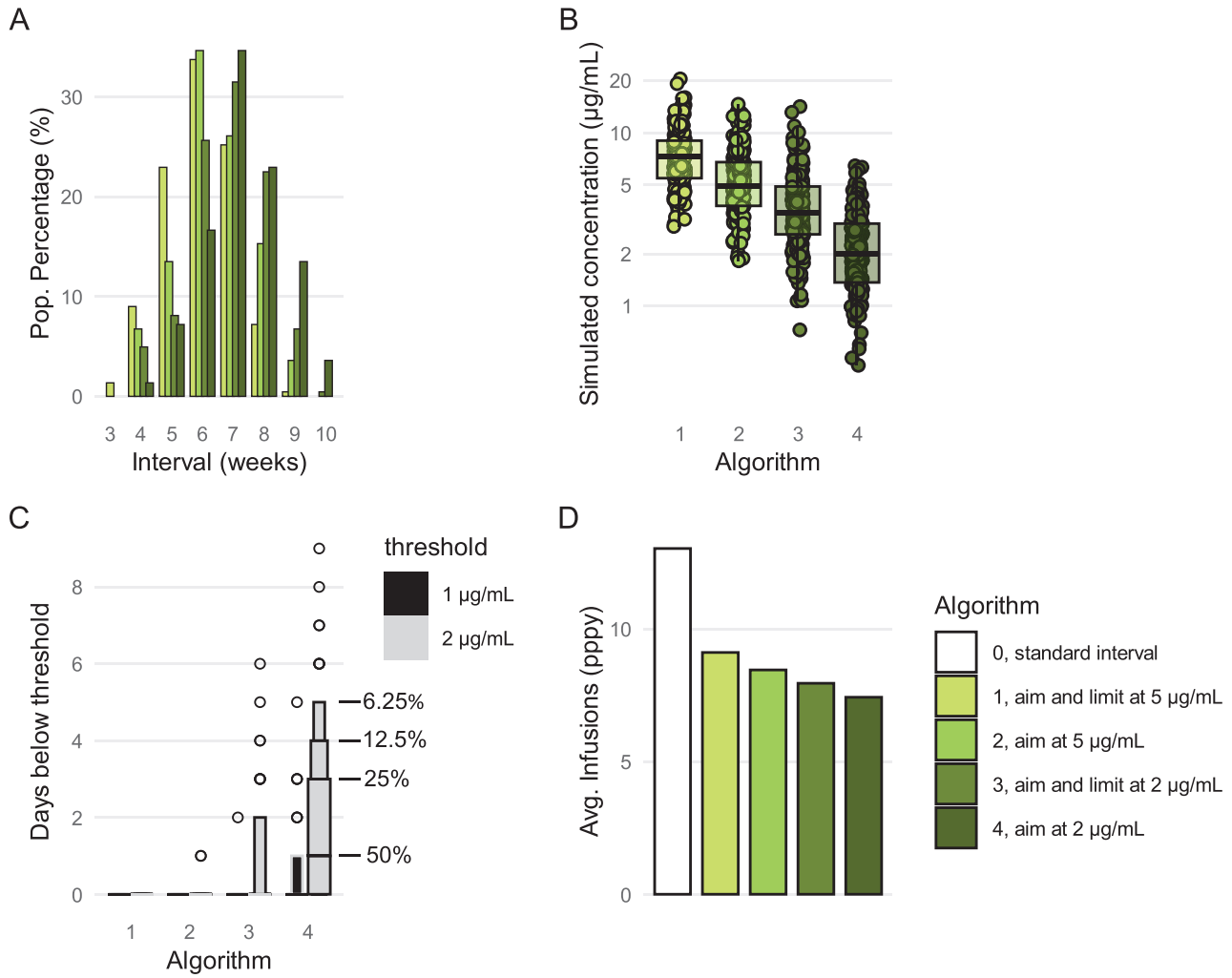

FIGURE 3 | Simulation of clinical implementation of four algorithms (1–4, color-coded) in a ascending order of risk using the final PK model. (A) Percentage of the population on a simulated personalized interval resulting from each algorithm. (B) Boxplot of simulated observed natalizumab concentrations at trough, which was defined as the individual prediction of trough concentration with a randomly sampled prediction error as previously identified. (C) Consecutive days within a dose interval with natalizumab concentrations falling below a threshold (2 or 1 µg/mL), shown with Letter-value Plots displaying quartiles (25%, 75%), octiles (12.5%, 87.5%) and hexadeciles (6.25%, 93.75%). (D) Mean infusions per person per year (pppy) of the algorithms versus standard interval dosing.

internalization bounded by natalizumab followed by intracellular degradation, or clearance of cells to which natalizumab is bound. Nonlinear elimination is the dominant clearance pathway at lower concentrations. However, the exact size of this pathway is unknown and complex, as α4-integrin expression is reduced with natalizumab exposure [12]. The final PK model estimated a lower K_m (0.875 µg/mL) than a previously published model, which could be due to further extension of dose intervals and subsequently lower trough samples, the absence of antidrug antibodies, or an erroneous simplification of target mediated drug disposition with Michaelis–Menten kinetics [23]. More measurements in the lower concentration range may improve estimation of saturable elimination and related kinetics. A limitation of our approach was that individuals were fitted only on two trough samples at the end of a 4-week interval. Therefore, the model was unable to discern whether a lower trough concentration, relative to the typical population, resulted from higher linear clearance, lower distribution volume, or increased saturable elimination. A potential solution involves incorporating measurements at various time points within the dosing interval or assessing trough concentrations at different intervals to enhance precision in individual PK parameters.

A disadvantage of i.v. dosing is the need for hospital visits, which can be overcome by subcutaneous (s.c.) dosing. The EMA accepted in 2023 natalizumab s.c. injections of two times 150 mg once every 4 weeks. If subcutaneous administration becomes a standard treatment, MIPD can also be effectively applied to it. Fingerpricks at home can be used for measurements facilitating TDM in this context, confirming sufficient drug exposure and improving the implementation of MIPD [25]. Moreover, the dosing regimen of s.c. injections is not confined to full weeks, permitting more flexible dose intervals. Shorter dose intervals are expected for s.c. versus i.v. administered natalizumab, as decreased bioavailability following s.c. reduces natalizumab exposure [26]. The prospective milestone would be MIPD informed by TDM with administration at home without the need for hospital visits.

In conclusion, MIPD would improve the precision of selecting individual dose intervals compared to a previously conducted TDM-guided protocol for personalized dosing. The findings support the superiority of MIPD, which tailors treatment for individuals, reducing hospital visits and lowering overall costs tremendously. Future research should investigate the cost-effectiveness and performance of MIPD in the clinic. Additionally, monitoring drug levels following precision dosing can be used to enhance individual PK estimates, enabling further refinement of dose intervals.

Author Contributions

S.P.H.B. wrote the manuscript. T.P.C.D., T.R., J.K., G.W., and Z.L.E.K. designed the research and analyzed the data. S.P.H.B., A.A.T., F.H., N.M.F.V., and L.M.Y.G. performed the research and analyzed the data.

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Conflicts of Interest

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.