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ORIGINAL RESEARCH ARTICLE

Treatment Targets Should Influence Choice of Infliximab Dose Intensification Strategy in Inflammatory Bowel Disease: A Pharmacokinetic Simulation Study

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Abstract

Background The optimal infliximab dose intensification strategy to address loss of response associated with subtherapeutic infliximab trough levels remains uncertain, as does whether post-intensification trough and treatment targets should influence this decision.

Objectives This pharmacokinetic simulation study aimed to identify infliximab dose intensification strategies capable of achieving post-intensification infliximab trough thresholds associated with clinical and objective treatment targets in Crohn's disease and ulcerative colitis.

Methods A validated pharmacokinetic infliximab model, applied to 200 simulated patients, identified those with subtherapeutic (< 3.00 mg/L) trough levels after 30 weeks of standard (5 mg/kg 8-weekly) dosing, and subsequently applied 10 dose intensification strategies over a further 32 weeks. The proportion of simulations achieving 32-week post-intensification infliximab trough levels associated with endoscopic remission (ulcerative colitis > 7.50 mg/L, Crohn's disease > 9.70 mg/L) was the primary outcome, with perianal fistula healing (Crohn's disease > 10.10 mg/L) and clinical improvement (ulcerative colitis > 3.70 mg/L, Crohn's disease > 7.00mg/L) evaluated as secondary outcomes. All outcomes were stratified by intensity of dose intensification, with standard (≤ 10 mg/kg 8-weekly or 5 mg/kg 4-weekly; $n = 5$) and intensive (> 10 mg/kg 8-weekly or 5 mg/kg 4-weekly; $n = 5$) dosing strategies defined, respectively.

Results The median pre-intensification infliximab trough level was 0.91 mg/L (interquartile range 1.37). Intensive dosing strategies were more likely to achieve infliximab trough concentrations associated with endoscopic remission (ulcerative colitis 36.48% vs. 10.80%, Crohn's disease 25.98 vs. 4.68%), perianal fistula healing (24.52% vs. 4.36%) and clinical improvement (ulcerative colitis 61.90% vs. 34.86%, Crohn's disease 40.32 vs. 12.08%) than standard intensification strategies (all $p < 0.01$). When controlling for cumulative (mg/kg) infliximab dose over 32 weeks, strategies that concurrently dose increased and interval shortened achieved the highest infliximab trough levels (all $p < 0.01$).

Conclusion This simulation-based analysis highlights the potential of using post-intensification infliximab trough thresholds associated with aspirational treatment targets in Crohn's disease and ulcerative colitis to guide choice of infliximab dose intensification strategy. Intensive dose intensification strategies, particularly those that concurrently dose increase and interval shorten, appear to achieve higher infliximab levels than standard dose intensification strategies. This may be particularly important in the pursuit of stringent endpoints, such as endoscopic remission and fistula healing, which have been consistently associated with higher infliximab trough levels. These findings require validation across real-world cohorts.

1 Introduction

Infliximab is an effective therapy for moderate to severe ulcerative colitis and Crohn's disease, including perianal fistulising manifestations [1–3]. However, secondary loss of response to standard maintenance dosing remains common, occurring in up to 37% of infliximab-treated patients within the first year of therapy, at an annualised risk of 13% per patient-year [4, 5]. Measuring infliximab trough levels at the time of loss of response, including appraisal of anti-infliximab antibodies (ATI), is well established, and intensified infliximab dosing is effective in overcoming loss of response associated with subtherapeutic infliximab trough levels, with or without low-titre ATI [5–7]. Commonly applied infliximab dose intensification strategies include one or more of

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Key Points

Whether treatment targets should influence the choice of infliximab dose intensification strategy in the setting of loss of response associated with subtherapeutic infliximab trough levels remains unclear.

This study examined the potential of using post-intensification infliximab trough thresholds associated with aspirational treatment targets in inflammatory bowel disease, to guide choice of infliximab dose intensification strategy.

Intensive (> 10 mg/kg 8-weekly or 5 mg/kg 4-weekly) dose intensification strategies were more likely to achieve infliximab trough concentrations associated with clinical, perianal and endoscopic treatment targets, than standard intensification strategies.

upfront re-induction, shortening the dosing interval and/or increasing the dose of infliximab administered [8–12]. However, a single strategy may not be universally successful across all clinical scenarios. This has led to marked variability in dose intensification practices owing to a relative paucity of data to assist clinicians in determining which infliximab dose intensification strategy to apply.

As treatment goals have evolved to include targets beyond symptom control alone, it remains important to acknowledge the relationship between objective endpoints such as biomarker normalisation, radiologic healing and endoscopic remission and higher infliximab levels, relative to clinical endpoints alone [13–15]. This has been reflected in studies documenting that to achieve aspirational treatment targets such as endoscopic remission, which has been endorsed by the STRIDE II guidelines, may require infliximab trough levels above 9.70 mg/L and 7.50 mg/L in Crohn's disease and ulcerative colitis, respectively [16–18]. Similarly, achieving fistula healing in perianal Crohn's disease has been associated with higher levels than luminal disease, with data indicating that levels above 10.10 mg/L may even be necessary [19]. Hence, determining which dose intensification strategies are capable of achieving infliximab trough thresholds associated with these treatment targets warrants further study. This is particularly important in the context of subtherapeutic infliximab trough levels where more intensive dosing strategies are frequently required to avoid pharmacokinetic treatment failure.

Drug clearance represents an important determinant of infliximab trough concentrations, with factors such as albumin, weight, sex, C-reactive protein (CRP), and ATI shown to influence infliximab clearance and consequent pharmacokinetic loss of response [20]. These parameters can be incorporated into pharmacokinetic infliximab models capable of simulating commonly applied infliximab dosing strategies to forecast infliximab trough concentrations at future timepoints. This study aimed to simulate the management of loss of response associated with subtherapeutic infliximab trough levels, and thus identify dose intensification strategies capable of achieving post-intensification trough level thresholds associated with treatment targets in Crohn's disease and ulcerative colitis.

2 Methods

A previously published, two-compartment population pharmacokinetic infliximab model, developed using 7169 concentration observations from 788 patients treated across six clinical trials, formed the basis of this study [21]. This model was chosen over other published infliximab models for the present work as it was based on one of the largest infliximab datasets, and included patients, most of whom had inflammatory bowel disease (IBD; $n = 655$), spanning a range of body sizes. This model was also used in the PRECISION trial [22]. The model was used to simulate standard intravenous infliximab induction (5 mg/kg weeks 0, 2, 6) followed by maintenance (5 mg/kg 8-weekly) dosing over 30 weeks (six doses). Those forecast to have subtherapeutic infliximab trough levels below 3.00 mg/L at week 30 were deemed at risk of pharmacokinetic-driven loss of response and thus represented the subgroup of interest in whom infliximab dose intensification was simulated.

2.1 Infliximab Dose Intensification Protocols

A total of 10 infliximab dose intensification protocols, reflective of one or both of shortening the interval between infliximab doses and increasing the infliximab dose, were simulated (Fig. 1). Infliximab dose intensification strategies that were simulated included 8-weekly (7.5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg), 6-weekly (5 mg/kg, 7.5 mg/kg, 10 mg/kg) and 4-weekly (5 mg/kg, 7.5 mg/kg, 10 mg/kg) dosing intervals. A baseline dosing strategy of 5 mg/kg 8-weekly (i.e. no dose intensification) was also simulated as the reference protocol. Each dose intensification regimen was administered to the same cohort of 200 simulated patients between weeks 30 and 62 with the aim of forecasting post-intensification infliximab trough levels after 30 (6-weekly) to 32 (4-weekly, 8-weekly) weeks of intensified dosing.

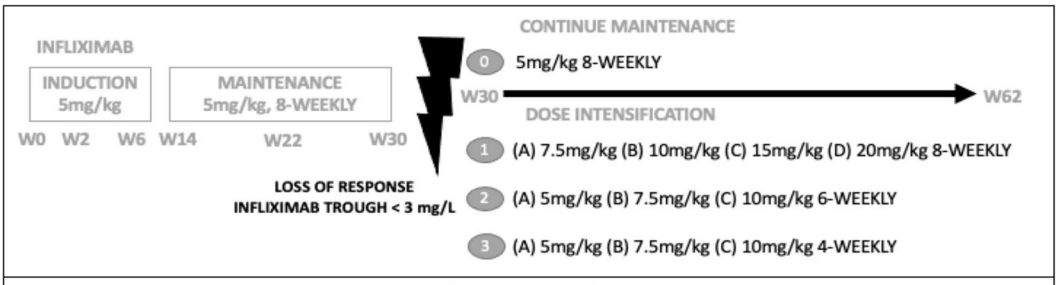
2.2 Model Parameters

Serum albumin (g/dL), weight (kg), and ATI parameters were simulated across 200 patients (Online Resource Table 1) and input into the pharmacokinetic infliximab model to determine infliximab trough levels following each of the 10 dose intensification strategies.

Simulated patients were generated with body weight sampled from a log-normal distribution centred on 70 kg and a log standard deviation (SD) of 0.09. Interindividual variability was log-normally distributed, and intraindividual variability in measured infliximab concentrations was described by a proportional residual error model. Serum albumin was sampled from a log-normal distribution centred on 4 g/dL and a log SD of 0.30. Model covariates included weight (on all population parameters) and serum albumin concentration (on clearance) as described by power models referenced to 70 kg and 4 g/dL, respectively, and the presence of ATI as a dichotomous relationship on clearance. The presence or absence of ATI was sampled from a binomial distribution, with a per-case ATI probability of 25% assigned, in keeping with published data indicating that ATI are present in 8–70% of infliximab-treated patients with IBD [23, 24]. Exploratory simulations were also performed to demonstrate the impact of lower (0%) and higher (50%) ATI probability on post-intensification infliximab trough levels.

2.3 Study Outcomes

Endoscopic remission has been endorsed by the STRIDE-II guidelines as a long-term treatment target in both Crohn's disease and ulcerative colitis [18, 25]. Hence, the primary outcome was defined as the proportion of simulated patients who achieved post-intensification infliximab trough levels associated with endoscopic remission after 32 weeks of intensified dosing. Secondary outcomes included the proportion of simulated patients achieving post-intensification infliximab trough levels associated with clinical improvement and perianal fistula healing. All outcomes were stratified by intensity of dose intensification to elucidate differences



CATEGORY	DOSING STRATEGY	INFLIXIMAB DOSE	DOSING INTERVAL
0	Continue standard maintenance dosing	5mg/kg	8-weekly
1a 1b 1c 1d	Dose increase	7.5mg/kg 10mg/kg 15mg/kg 20mg/kg	8-weekly
2a 2b 2c	Dose increase AND Dose interval shortening	5mg/kg 7.5mg/kg 10mg/kg	6-weekly
3a 3b 3c	Dose increase AND Dose interval shortening	5mg/kg 7.5mg/kg 10mg/kg	4-weekly

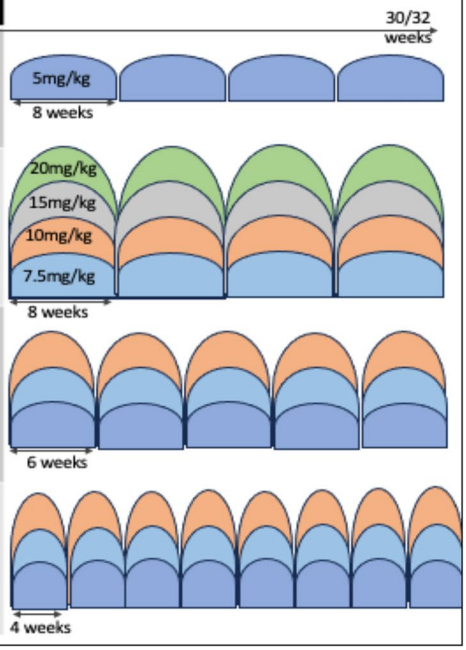


Fig. 1 Infliximab dosing schema depicting 10 infliximab dose intensification strategies applied in pharmacokinetic simulations. *W* week

between intensive and standard dose intensification strategies in achieving aspirational infliximab trough targets from a subtherapeutic baseline. The impact of pre-intensification antibody status on post-intensification infliximab levels was also evaluated.

2.4 Definitions

The lower limit of the therapeutic infliximab trough level range was defined as 3.00 mg/L, with levels below this threshold deemed subtherapeutic [26]. Infliximab trough levels associated with endoscopic remission in ulcerative colitis and Crohn's disease were defined as above 7.50 mg/L and 9.70 mg/L, respectively, based on previously published data (Table 1) [16, 17]. Infliximab trough levels associated with clinical improvement were defined as above 3.70 mg/L and 7.00 mg/L in ulcerative colitis and Crohn's disease, respectively [27, 28]. Finally, infliximab trough levels associated with perianal fistula healing in Crohn's disease were defined as above 10.10 mg/L [19]. We acknowledge that various infliximab thresholds have been associated with these outcomes; however, these thresholds were chosen to reflect among the highest reported trough thresholds based on a published review [29]. Early trough levels following intensification were assessed at 12, 14 or 16 weeks, while sustained trough levels were assessed at weeks 30 or 32 (as dictated by the trough times for each dose regimen). Dose intensification strategies that applied a dose of > 10 mg/kg 8-weekly or equivalent (e.g. > 7.5 mg/kg 6-weekly or > 5 mg/kg 4-weekly) over 32 weeks were defined as 'intensive' (Table 2). Standard dose intensification strategies, that is any strategy that applied 10 mg/kg 8-weekly or less over 32 weeks, frequently represent first-line dose intensification strategies to address loss of response in clinical practice, with more intensive strategies generally applied in the event that standard dose intensification strategies do not achieve desired treatment targets. Hence, the purpose of differentiating between intensive and standard dose intensification strategies was to identify situations where intensive dose intensification may have utility as a first-line approach ahead of standard intensification strategies.

2.5 Software

All statistical and graphical analyses were performed using the R statistical and programming language (R Core Team 2021, version 4.0.5). Non-parametric tests were chosen as the data were not normally distributed, with or without log transformation. Data were summarised via medians and interquartile ranges (IQR). Comparison of trough concentrations was assessed by Wilcoxon signed-rank (paired data) or Wilcoxon rank-sum tests (unpaired data) in R. A proportions test was used to compare percentages. A p value of < 0.05 was considered statistically significant throughout all analyses.

Table 2 Standard versus intensive infliximab dose intensification strategies applied in pharmacokinetic simulations

Standard ≤ 10 mg/kg, 8-weekly		Intensive > 10 mg/kg, 8-weekly	
1a	7.5 mg/kg 8-weekly	1c	15 mg/kg 8-weekly
1b	10 mg/kg 8-weekly	1d	20 mg/kg 8-weekly
2a	5 mg/kg 6-weekly	2c	10 mg/kg 6-weekly
2b	7.5 mg/kg 6-weekly	3b	7.5 mg/kg 4-weekly
3a	5 mg/kg 4-weekly	3c	10 mg/kg 4-weekly

Table 1 Aspirational 'treat-to-trough' infliximab thresholds associated with treatment targets in inflammatory bowel disease

Infliximab trough threshold	Treatment outcome	Definition
3.00 mg/L [26]	Lower limit of therapeutic threshold	
> 3.70 mg/L [28]	Clinical response Ulcerative colitis	Decrease in the total Mayo score of ≥ 3 points and ≥ 30%, and an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or an absolute subscore of 0 or 1
> 7.00 mg/L [27]	Clinical remission Crohn's disease	Harvey Bradshaw Index ≤ 4, no ongoing steroid therapy, and CRP ≤ 3 mg/L
> 7.50 mg/L [16]	Endoscopic remission Ulcerative colitis	Mayo endoscopic subscore ≤ 1
> 9.70 mg/L [17]	Endoscopic remission Crohn's disease	Absence of any mucosal break (ulceration or erosion) or for patients with an ileocolonic resection, a Rutgeerts score of ≤ 1
> 10.10 mg/L [19]	Perianal fistula healing Crohn's disease	Absence of fistula drainage without a seton

CRP C-reactive protein

3 Results

3.1 Model Validation

The pharmacokinetic model was validated by comparing model predictions with data from a previously published prospective dose intensification study [30]. The cohort used for comparison comprised 50 IBD patients who were dose-intensified from 5 mg/kg 8-weekly to 5 mg/kg 6-weekly over 30 weeks to address secondary loss of response. Infliximab trough concentrations before and after dose intensification were compared between the model and real-world study data. This was undertaken by simulating 200 patients subjected to the same dosing change as the study over 30 weeks and comparing post-intensification infliximab trough levels at weeks 0, 6, 12 and 30 between the pharmacokinetic model and study data. The body weight, albumin levels, and ATI status for each of the 200 patients were sampled from log-normal or binomial distributions that closely matched the parameters of patients enrolled in the clinical study. A visual predictive check (VPC) was used to compare the observed and simulated data (Fig. 2) [31].

There was good agreement between observed and simulated data both at baseline (week 0) and in representing the accumulation of infliximab over 32 weeks of dose intensification. Furthermore, VPCs conditioned on age, sex, prior biological failure, disease duration, IBD subtype (Crohn's disease vs. ulcerative colitis), immediate response, prior immunomodulator use, objective disease activity immediately prior to dose intensification, duration of infliximab therapy prior to dose intensification, and sustained response following dose intensification, all showed good agreement between observed and predicted data, suggesting that none of these factors were needed as additional covariates in the model. On this basis, the pharmacokinetic model was deemed fit for the purpose of simulating different infliximab dose intensification strategies as a means of forecasting post-intensification infliximab trough levels in patients with IBD.

3.2 Impact of Infliximab Dose Intensification on Infliximab Trough Levels

The median infliximab trough level immediately prior to dose intensification was 0.91 mg/L (IQR 1.37) and the median infliximab trough level 30–32 weeks following dose intensification was 3.58 mg/L (IQR 5.69; $p < 0.01$). Median infliximab trough levels were comparable at weeks 12–16 (3.43 mg/L, IQR 5.50) and 30–32 (3.58 mg/L, IQR 5.69) across all dose intensification strategies. All 10 dose intensification strategies were able to achieve infliximab trough levels above 3.00 mg/L across 56.14% of post-intensification simulations by week 32, with 6 of 10 regimens able to achieve a median post-intensification infliximab trough concentration above this threshold.

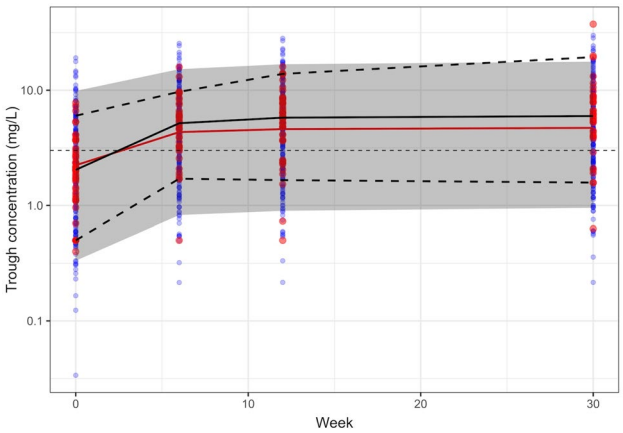


Fig. 2 A visual predictive check of the observed and simulated validation data. The observed and simulated data are shown by red and blue symbols, respectively. The solid black line is the median of the observed data, while the dashed black lines are the 90% prediction interval of the observed data. The 90% prediction intervals of the simulated data are shown by the grey ribbon and the median of the simulated data is shown by the red line

3.3 Impact of Infliximab Dose Intensification Strategy on Infliximab Trough Levels

Five of the 10 strategies met the criteria for 'intensive' dose intensification. The median infliximab trough level 32 weeks following intensive dose intensification was higher than following standard dose intensification (5.64 [IQR 7.49] vs. 2.51 [IQR 3.45] mg/L; $p < 0.01$). This was reflected by a higher proportion of simulated patients achieving aspiration infliximab trough targets (at 30/32 weeks) associated with endoscopic remission (> 7.50 mg/L: 41.1 vs. 10.3%; > 9.7 mg/L: 29.8 vs. 4.44%; each $p < 0.01$), perianal fistula healing (> 10.10 mg/L: 28.6 vs. 4.26%; $p < 0.01$) and clinical improvement (> 3.70 mg/L: 67.3 vs. 30.8%; > 7.00 mg/L: 45.0 vs. 11.08%; each $p < 0.01$) following intensive relative to standard dose intensification.

When comparing dose intensification strategies that administered the same cumulative infliximab dose (mg/kg) over 32 weeks, strategies that shortened the dosing interval had higher infliximab trough levels by week 32 compared with strategies that simply increased the dose. Similarly, strategies that did both, that is shortened the dosing interval and increased the dose administered, achieved the highest trough levels. This was most apparent when comparing the median week 32 infliximab trough level across 8-weekly 10 mg/kg (1.83 mg/L), 15 mg/kg (2.74 mg/L) and 20 mg/kg (3.65 mg/L) dosing strategies with 4-weekly 5 mg/kg (5.98 mg/L), 7.5 mg/kg (8.96 mg/L) and 10 mg/

kg (11.9 mg/L), respectively (all $p < 0.01$). These data are summarised graphically in Fig. 3.

3.4 Outcome of Infliximab Dose Intensification Stratified by Treatment Target

The proportion of simulated patients who achieved infliximab levels associated with clinical and endoscopic treatment targets using each infliximab dose intensification strategy are summarised in Fig. 4. The pharmacokinetic profile of each dose intensification strategy over 32 weeks is depicted in Fig. 5a.

3.4.1 Endoscopic Remission

3.4.1.1 Ulcerative Colitis Seven (70%) dose intensification strategies achieved infliximab trough levels above 7.50 mg/L, across 23.64% of dose-intensified simulations by week 32. Only two strategies (7.5 mg/kg 4-weekly [56.50%] and 10 mg/kg 4-weekly [70.20%]), both of which were intensive, were able to exceed this threshold in more than 50% of simulated patients.

3.4.1.2 Crohn's Disease Five (50%) dose intensification strategies were able to achieve a mean infliximab trough level above 9.70 mg/L, across 15.33% of dose-intensified simulations by week 32. Only one strategy (10 mg/kg 4-weekly [58.10%]), which was intensive, was able to exceed this threshold in more than 50% of simulated patients.

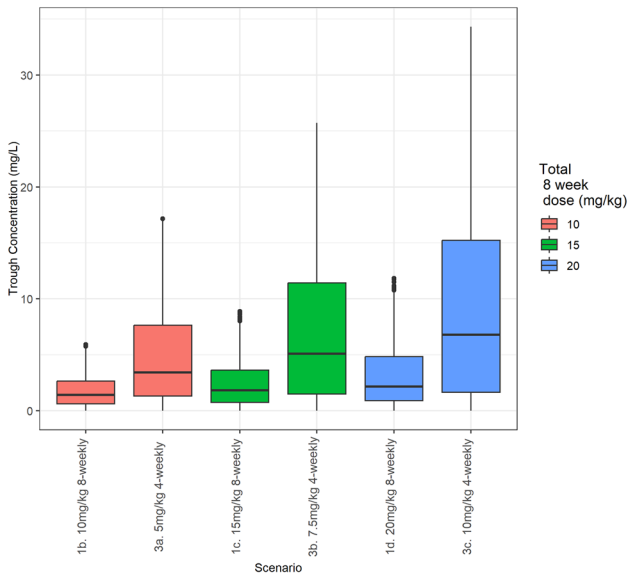


Fig. 3 Impact of infliximab dose intensification strategy on week 32 infliximab trough levels when controlling for cumulative infliximab dose (mg/kg) over 32 weeks. The features of the boxplots are: lower hinge = 25% quantile, middle = median (50% quantile), upper hinge = 75% quantile, lower whisker = lower hinge − 1.5 * IQR, upper whisker = upper hinge + 1.5 * IQR. Outliers outside the lower and upper whiskers are shown as points. *IQR* interquartile range

3.4.2 Clinical Improvement

3.4.2.1 Ulcerative Colitis All 10 dose intensification strategies were able to achieve infliximab levels above 3.70 mg/L, across 48.38% of dose-intensified simulations by week 32. Four strategies (10 mg/kg 6-weekly [51.60%], 5 mg/kg 4-weekly [71.00%], 7.5 mg/kg 4-weekly [83.90%] and 10 mg/kg 4-weekly [87.70%]), three of which were intensive, were able to achieve this threshold in more than 50% of patients.

3.4.2.2 Crohn's Disease Seven (70%) dose intensification strategies were able to achieve infliximab levels above 7.00 mg/L, across 26.20% of dose-intensified simulations by week 32. Two strategies (7.5 mg/kg 4-weekly [59.70%] and 10 mg/kg 4-weekly [74.20%]), both of which were intensive, were able to achieve this threshold in more than 50% of patients.

3.4.3 Perianal Fistula Healing

Five (50%) dose intensification strategies were able to achieve infliximab trough levels above 10.10 mg/L, across 14.44% of dose-intensified simulations by week 32. Only one strategy, namely 10 mg/kg 4-weekly (55.60%), was able to exceed this threshold in more than 50% of patients.

3.5 Impact of Antibody Status

Patients simulated to have ATI prior to dose intensification had lower median infliximab trough levels (2.94 mg/L, IQR 4.49 mg/L) following dose intensification compared with those without ATI (3.93 mg/L, IQR 6.26 mg/L), across all dose intensification strategies ($p < 0.01$) (Fig. 5b). The difference in median infliximab trough levels between simulations with and without ATI when applying the same dose intensification strategy was 0.99 mg/L. When the initial probability of ATI across the simulated cohort was reduced to 0%, there was a noticeable increase in median week 30/32 infliximab trough levels across the entire simulated cohort relative to the base (ATI 25%) simulation (4.04 [IQR 6.07] vs. 3.58 [IQR 5.69] mg/L; $p < 0.001$) [Online Resource Table 2a]. Conversely, when the probability of ATI was increased to 50%, there was no significant change in infliximab trough levels across all dose intensification regimens compared with the base (ATI 25%) simulation (3.51 [IQR 5.65] vs. 3.58 [IQR 5.69] mg/L; $p = 0.71$) [Online Resource Table 2b]. This lack of difference most likely reflects the censoring for enrolment into the study (baseline trough < 3.00 mg/L) that selects high-clearance patients.

Simulation Category	Infliximab dose & interval	Median Infliximab level mg/L [IQR]	>3.0 mg/L	>3.7 mg/L	>7.0 mg/L	>7.5 mg/L	>9.7 mg/L	>10.1 mg/L
STANDARD STRATEGIES	≤10mg/kg 8-weekly	2.51 [3.45]	43.4%	34.9%	12.1%	10.8%	4.7%	4.4%
INTENSIVE STRATEGIES	>10mg/kg 8-weekly	5.64 [7.49]	68.9%	61.9%	40.3%	36.5%	26.0%	24.5%
0	5mg/kg 8 weekly	0.91 [1.37]	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1a STANDARD	7.5mg/kg 8 weekly	1.37 [2.06]	21.0%	8.9%	0.0%	0.0%	0.0%	0.0%
1b STANDARD	10mg/kg 8 weekly	1.83 [2.75]	32.3%	24.2%	0.0%	0.0%	0.0%	0.0%
1c INTENSIVE	15mg/kg 8 weekly	2.74 [4.13]	46.0%	37.1%	12.1%	8.1%	0.0%	0.0%
1d INTENSIVE	20mg/kg 8 weekly	3.65 [5.51]	57.3%	49.2%	26.6%	24.2%	10.5%	8.1%
2a STANDARD	5mg/kg 6 weekly	2.08 [2.59]	35.5%	25.0%	0.0%	0.0%	0.0%	0.0%
2b STANDARD	7.5mg/kg 6 weekly	3.12 [3.87]	50.0%	45.2%	16.9%	14.5%	0.0%	0.0%
2c INTENSIVE	10mg/kg 6 weekly	4.16 [5.15]	60.5%	51.6%	29.0%	23.4%	15.3%	13.7%
3a STANDARD	5mg/kg 4 weekly	5.98 [5.95]	78.2%	71.0%	43.5%	39.5%	23.4%	21.8%
3b INTENSIVE	7.5mg/kg 4 weekly	8.96 [8.94]	87.9%	83.9%	59.7%	56.5%	46.0%	45.2%
3c INTENSIVE	10mg/kg 4 weekly	11.9 [11.93]	92.7%	87.7%	74.2%	70.2%	58.1%	55.6%

Proportion of patients achieving pre-specified infliximab trough threshold			
0.1 – 25.0%	25. 1 – 50.0%	50.1 – 75.0%	75. 1 – 100.0%

Fig. 4 Proportion of simulated patients achieving aspirational infliximab trough level targets following 32 weeks of intensified dosing when applying a 25% probability of developing antibodies to infliximab. *IQR* interquartile range

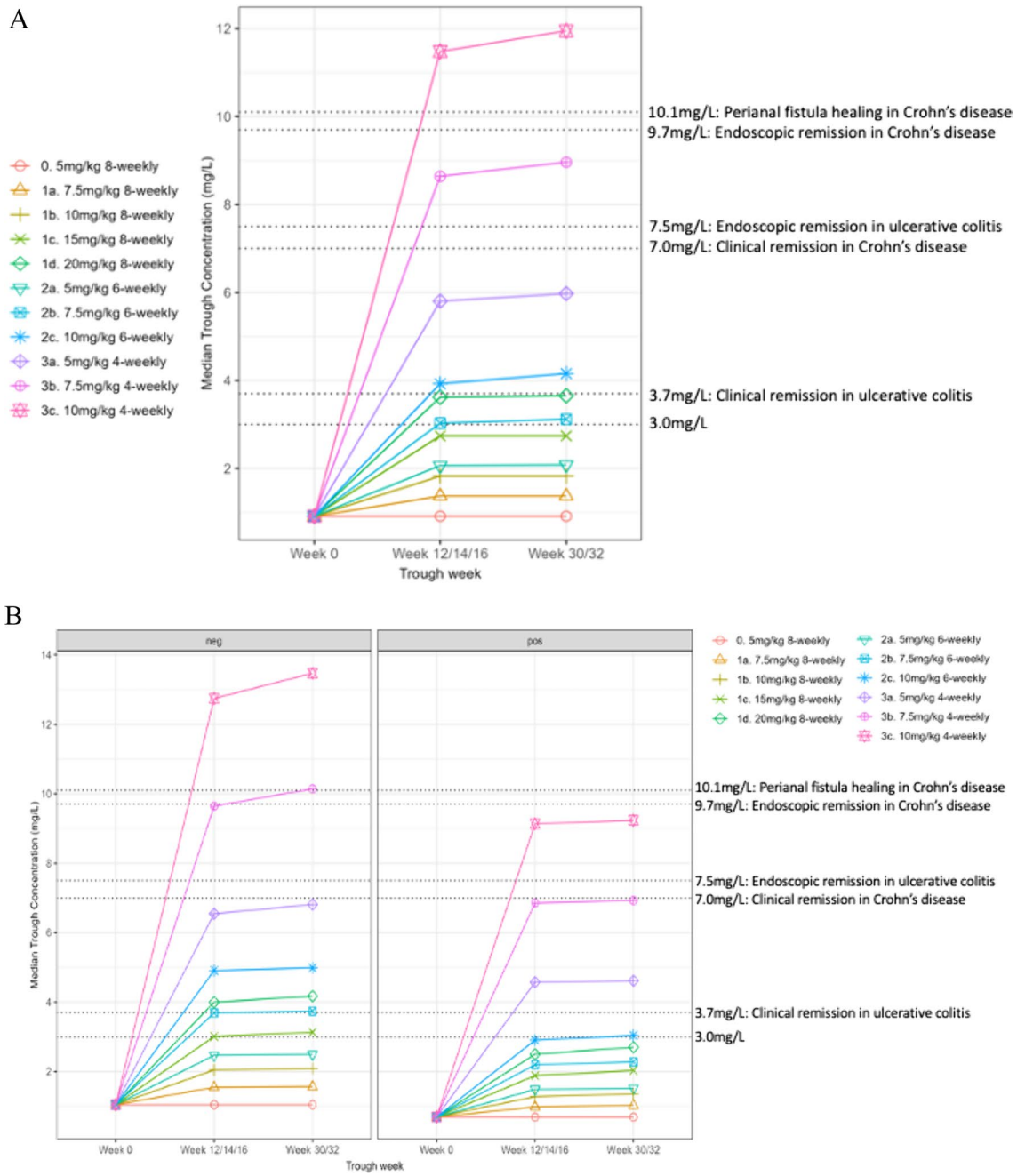


Fig. 5 (**a**) Infliximab trough concentrations by dose intensification strategy with each clinically relevant threshold level represented. (**b**) Infliximab trough concentrations by dose intensification strategy with each clinically relevant threshold level represented, stratified by presence of antibodies to infliximab

4 Discussion

This study represents the first simulation-based analysis to benchmark post-intensification infliximab trough levels with those associated with IBD treatment targets in the context of managing loss of response associated with subtherapeutic trough levels. Our findings reflect that intensive infliximab dose intensification strategies are more likely to achieve post-intensification infliximab trough thresholds associated with stringent treatment targets such as endoscopic remission and perianal fistula healing, than standard dose intensification strategies. When controlling for cumulative infliximab dose administered, dose intensification strategies that combined a dose increase with a shortened dosing interval achieved the highest infliximab trough levels. These findings affirm that a dose

intensification strategy represents a key determinant of post-intensification trough levels.

The pharmacokinetic model applied in this study was validated against data from a published prospective infliximab dose intensification study, providing reassurances regarding the reliability of infliximab levels forecast on the basis of pharmacokinetic modelling [30]. Unlike 'real-world' studies to date, this simulation study was able to compare multiple standard and intensive dose intensification strategies across a single cohort of, albeit simulated, patients. Notably, there were no differences between short-term (weeks 12–16) and sustained (weeks 30–32) infliximab levels across all 10 dose intensification strategies, implying that early assessment of post-intensification infliximab levels may be of similar utility to those assessed at later timepoints. This is supported by recent research from our group that demonstrated the utility of early post-intensification infliximab levels in differentiating between future clinical response and non-response [30]. The model also demonstrated that the presence of ATI prior to dose intensification was associated with lower infliximab trough levels following dose intensification; reinforcing the significance of ATI at the time of loss of response. Collectively, these findings imply that pre-intensification infliximab trough levels, including antibody status, and post-intensification trough and treatment targets, all represent important considerations when selecting an infliximab dose intensification strategy to address low trough levels.

The most clinically novel aspect of this simulation study is the first-time application of a treat-to-trough approach to infliximab dose intensification in the pursuit of post-intensification infliximab trough targets associated with treatment targets endorsed by the STRIDE II guidelines. Nevertheless, several study limitations must also be acknowledged. First, infliximab trough thresholds used in our analysis were based on associations rather than causation; therefore, a subgroup of patients may still have achieved target endpoints with lower infliximab levels. While the concept of attributing an absolute threshold to a desired treatment target is clinically desirable, achieving a prespecified threshold in this context is more likely to reflect a probability, rather than guarantee, of success. We also chose to focus on thresholds that were among the highest in the published literature, potentially underestimating the likelihood of treatment success across evaluated targets. Second, the impact of ATI on post-intensification infliximab levels is unlikely to be binary, but rather dependent on antibody titre in the context of the infliximab assay used. While our model did evaluate the impact of different thresholds of ATI on post-intensification trough levels, the impact of neutralising versus non-neutralising ATI, and transient ATI, could not be evaluated. Third, the simulation assumed infliximab monotherapy during the induction, maintenance, and intensification phases. This does not always reflect clinical practice wherein infliximab is frequently used in combination with an immunomodulator, particularly in cases at risk of pharmacokinetic failure [32]. Fourth, our model did not incorporate several patient, disease, and biochemical characteristics such as smoking status, age, disease severity, steroid use, CRP, body composition, prior biologic failure, and genetic polymorphisms, which have been associated with infliximab pharmacokinetics and post-intensification clinical outcomes [5]. Similarly, the pharmacokinetic model did not integrate faecal calprotectin which, on the basis of a recent study, may enhance the clinical applicability of future pharmacokinetic infliximab models [33].

The absence of quality data linking higher infliximab trough levels with unfavourable safety outcomes should embolden clinicians to apply intensive infliximab dosing regimens [34, 35]. We do however acknowledge the impact that such an approach might have on drug costs, even in the biosimilar era, highlighting the need to clinically rationalise the choice of dose intensification strategy in this context. It is also important to consider the potential impact that subcutaneous infliximab preparations, with putatively higher and more stable infliximab drug levels compared with the peak to trough variability of intravenous dosing, may have on rates of pharmacokinetic-mediated loss of response [36]. In light of more predictable pharmacokinetics, it remains plausible that subcutaneous infliximab formulations may be associated with a lower incidence of loss of response driven by immunogenicity compared with intravenous infliximab dosing, potentially obviating the need for as-frequent dose intensification. However, the clinical utility of switching from intravenous to subcutaneous infliximab administration in the setting of pharmacokinetic loss of response remains to be clarified. A recent simulation study that evaluated the pharmacokinetic profile of transitioning from intravenous to subcutaneous infliximab in patients with IBD highlighted that pharmacokinetic modelling may assist in this evaluation [37].

The PRECISION trial demonstrated that a dashboard-driven approach to infliximab dosing, focused on maintaining a trough concentration of 3 mg/L during maintenance therapy, was associated with higher rates of sustained clinical remission beyond 12 months ($p = 0.017$) and lower faecal calprotectin ($p = 0.031$), than continued infliximab therapy without dose or interval adjustments [22]. It is however important to acknowledge that clinicians frequently target infliximab trough levels much higher than 3 mg/L, particularly in the pursuit of stringent endpoints such as endoscopic remission and perianal fistula healing, both of which were evaluated in the present study. Moreover, a proactive approach to dose optimisation, that is optimisation of infliximab trough levels in the absence of clinical and objectively

confirmed disease, cannot be universally recommended on the basis of current evidence [38, 39]. Yet the targeted application of a proactive approach, particularly among high-risk patients such as those who experience pharmacokinetic loss of response, may hold merit and thus warrants further investigation. This is supported by data from Papamichael and colleagues that demonstrated that adopting a proactive approach to infliximab dose optimisation following an initial reactive approach, in the setting of presumed loss of response, was associated with improved drug persistence and fewer IBD-related hospitalisations compared with a reactive strategy alone [40]. Hence, the targeted application of a dashboard-driven approach capable of individualising infliximab dosing to achieve designated post-intensification infliximab trough thresholds may be particularly useful in this context and should thus be the focus of future research.

5 Conclusion

The complex, multifaceted nature of managing loss of response warrants a nuanced, tailored approach, and therefore may not be conducive to randomised controlled trial-based assessment [41]. This study adopted a pragmatic pharmacokinetic simulation based approach to identify the optimal infliximab dose intensification strategy to address loss of response associated with subtherapeutic infliximab trough levels. Our findings indicate that intensive dose intensification strategies, particularly those that concurrently dose increase and interval shorten, are more likely to achieve higher post-intensification infliximab trough levels than standard dose intensification strategies. This may be of particular importance in the pursuit of stringent IBD targets such as endoscopic remission and perianal fistula healing which have consistently been associated with higher infliximab trough levels than clinical outcomes alone; however these findings require validation across real-world cohorts. This study also examined, for the first time, the potential value of applying a treat-to-trough approach to infliximab dose intensification focused on achieving post-intensification infliximab trough levels associated with aspirational IBD treatment targets. However, uncertainty regarding the clinical and cost effectiveness of proactively targeting infliximab trough thresholds, including a lack of expert consensus regarding the optimal infliximab trough cut-offs associated with IBD treatment targets, implies that further studies are needed before existing algorithms pertaining to the management of loss of response can be updated.

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Declarations

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Conflicts of interest AS has served as a speaker for Sandoz and Arrowtex Pharmaceuticals, and has received advisory fees from Abbvie, Amgen, Arrotex Pharmaceuticals, Pfizer, and Takeda Pharmaceuticals. DvL has received educational grants or research support from Pfizer, Takeda, Ferring, and Shire, and has received consultancy and/or speaker's fees from Pfizer, Janssen, AbbVie, Ferring, Vifor and Emerge Health. PDC has served as a consultant, an advisory board member, or a speaker for AbbVie, Baxter, Ferring, Janssen, Celltrion, Pfizer, Emerge Health, Shire and Takeda; is supported by an NHMRC Emerging Leader 2 Fellowship; and has received research support from AbbVie, Ferring, Shire, Janssen, Pfizer and Takeda. JS has received speaker and/or conference fees from Pfizer, Takeda Pharmaceuticals, BMS, Sandoz, Abbvie, and Celltrion, and an unrestricted grant from Tillots. AV has received advisory fees from Abbvie. RU is a paid contractor for iDose, a developer of Bayes dosing software for infliximab.

Author contributions AS conceptualised the study. AS and RU undertook modelling and data analysis. AS reviewed the literature and prepared the original manuscript. All authors critically appraised and approved the final manuscript prior to submission.

Ethics approval This simulation study did not involve the use of patient data.

Consent to participate Not applicable.

Consent for publication Not applicable.

Data accessibility statement The data supporting the findings of this study may be provided upon reasonable request to the corresponding author subject to approval from our Institutional Review Board.

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