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ORIGINAL ARTICLE

Characterisation of individual ferritin response in patients receiving chelation therapy

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Aims: To develop a drug–disease model describing iron overload and its effect on ferritin response in patients affected by transfusion-dependent haemoglobinopathies and investigate the contribution of interindividual differences in demographic and clinical factors on chelation therapy with deferiprone or deferasirox.

Methods: Individual and mean serum ferritin data were retrieved from 13 published studies in patients affected by haemoglobinopathies receiving deferiprone or deferasirox. A nonlinear mixed effects modelling approach was used to characterise iron homeostasis and serum ferritin production taking into account annual blood consumption, baseline demographic and clinical characteristics. The effect of chelation therapy was parameterised as an increase in the iron elimination rate. Internal and external validation procedures were used to assess model performance across different study populations.

Results: An indirect response model was identified, including baseline ferritin concentrations and annual blood consumption as covariates. The effect of chelation on iron elimination rate was characterised by a linear function, with different slopes for each drug (0.0109 [90% CI: 0.0079–0.0131] *vs*. 0.0013 [90% CI: 0.0008–0.0018] L/mg mo). In addition to drug-specific differences in the magnitude of the ferritin response, simulation scenarios indicate that ferritin elimination rates depend on ferritin concentrations at baseline.

Conclusion: Modelling of serum ferritin following chronic blood transfusion enabled the evaluation of drug-induced changes in iron elimination rate and ferritin production. The use of a semi-mechanistic parameterisation allowed us to disentangle disease-specific factors from drug-specific properties. Despite comparable chelation mechanisms, deferiprone appears to have a significantly larger effect on the iron elimination rate than deferasirox.

KEYWORDS
chelating agents, deferasirox, deferiprone, disease modelling, ferritin, pharmacokinetic–pharmacodynamic relationships, thalassaemia

Elisa Borella and Sean Oosterholt contributed equally to this investigation.

1 | INTRODUCTION

Iron overload is one of the most relevant complications occurring in patients affected by rare haemoglobinopathies, whose survival depends on the use of frequent, sustained transfusions. Whereas in normal physiological conditions, uptake of iron into cells is controlled by the interaction of transferrin with its receptors, in iron overload conditions transferrin becomes saturated and iron species that are not bound to transferrin are present in plasma (plasma nontransferrin-bound iron, or NTBI). Organ damage in transfusional iron overload reflects therefore tissue iron uptake from NTBI, which promotes the generation of free radicals, causing tissue damage, and saturation of ferritin storage capacity, which in turn induces ferritin degradation by lysosomes and formation of an insoluble iron complex, i.e. haemosiderin, leading to organ toxicity.[1,2]

As a consequence, therapy with chelating agents is essential to promote iron extraction, clearing plasma from NTBI, removal of iron from cells and restoring body iron content to normal levels. In addition, clinical management is complemented by assessing iron accumulation in vital organs such as liver and heart for the prevention of long-term complications. However, routine monitoring of clinical labs (e.g. ferritin) remains critical for patients undergoing chelation therapy. In fact, clinical guidelines recommend serial measurement of serum ferritin at regular intervals.[3,4]

Irrespective of the debate about the role of serum ferritin as a biomarker for iron overload,[3–6] inferences about treatment response as well as accurate interpretation of absolute serum ferritin values remain challenging due to the unavailability of accepted algorithms or markers of response to chelating agents. For instance, one could interpret the lack of an initial drop in ferritin levels after the onset of treatment as an inadequate response to chelation therapy. However, this does not imply treatment failure or the absence of a long-term effect on iron burden.[5] Such a limitation makes it difficult for physicians to identify the need for dose adjustment or even modification of the chelation regimens, which should ultimately lead to stable, significant reduction in ferritin levels.[6]

Interestingly, to date the only report on the dynamic storage of iron in ferritin has not considered iron accumulation in longitudinal terms.[7] Specifically, the authors have developed a model in which ferritin operates as a high-capacity, iron buffer that maintains mobile iron concentrations until transcriptional or translational regulatory processes occur (e.g. changes in ferritin synthesis). However, their analysis does not incorporate the interaction between ferritin and chelating agents. In contrast to the predictions from this dynamic iron storage model, when patients are treated with chelating agents, there is a lag in the observed ferritin response, which depends not only on inter-individual differences in drug exposure and frequency and volume of blood transfused, but also on the turnover of the ferritin itself.[8] Consequently, for a given iron load, there is a considerable delay between the onset of treatment with chelating agents and achievement of a new steady state for ferritin.

Here we explore the feasibility of developing a drug–disease model to describe serum ferritin trajectories at population and individual patient level and assess the predictive performance of a model-based algorithm to predict individual ferritin response to chelation therapy. Differently from current clinical practice, which relies on the evaluation of serial serum ferritin measurements relative to baseline, we apply pharmacokinetic–pharmacodynamic principles to characterise iron homeostasis and ferritin production in patients affected by transfusion-dependent haemoglobinopathies. Our approach aims to describe the exposure–response relationships of two chelating agents (deferasirox and **deferiprone**) with relatively similar mechanisms of action using serum ferritin as a marker of treatment response in young children, for whom the use of organ biopsy or noninvasive imaging technologies is hindered by ethical and/or practical considerations.[3–6] It can be anticipated that the availability of such a model will provide a more robust basis for systematic prediction of an individual patient's need for dose adjustment before changes in serum ferritin are detected.

The focus on deferiprone and deferasirox is based on the fact that both are oral chelators and have been extensively studied in adults, in whom they both proved to have significant benefits regarding life quality improvements compared to parenteral administration of deferoxamine. In addition, both drugs have been recently evaluated in

What is already known about this subject

- Iron overload is one of the most relevant complications occurring in patients affected by haemoglobinopathies.
- As a consequence, therapy with chelating agents is essential to promote iron extraction, clearing plasma from nontransferrin-bound iron, removal of iron from cells and restoring body iron content to normal levels.
- To date, the effect of chelating agents on iron overload and resulting ferritin response has not been fully characterised.

What this study adds

- A drug–disease model describing ferritin response to iron chelation in chronically transfused patients with iron overload was developed taking into account blood consumption, iron elimination and ferritin production.
- In addition to the effect of variable blood consumption, baseline serum ferritin was found to contribute significantly to interindividual differences in ferritin response to iron chelators.
- Deferiprone appears to have a significantly larger effect than deferasirox on the iron elimination rate, and consequently on ferritin response.

retrospective and prospective studies in the paediatric population, where their benefit–risk profiles appeared to be similar.[9–11] Moreover, differently from deferoxamine, which exerts its action by inducing ferritin entry into lysosomes, deferiprone and deferasirox target cytosolic iron, thus preventing its incorporation into ferritin. Consequently, the availability of two chelating agents with similar mechanism of action provides an opportunity to identify model parameterisation that disentangles drug-specific from systems or disease-specific properties.

2 | METHODS

2.1 | Clinical data

Given that individual patient-level data were limited for the purposes of this analysis, a meta-analytical approach was used. A systematic review of the published literature was performed for 1990–2010, including studies in adult or paediatric patients with transfusion-dependent haemoglobinopathies, especially β-thalassemia major. Literature search was performed using PubMed, and included the following keywords and MESH terms: 'thalassemia', 'serum ferritin', 'iron overload', 'deferiprone', 'deferasirox', 'chelation therapy'. From the 88 publications identified in the initial screening, we have selected 20 studies which included mean or individual serum ferritin levels over time and in which deferasirox and/or deferiprone were used as monotherapy.[12–31]

From the available publications, 13 articles were selected for model development and 7 for model external validation. Serum ferritin profiles in untreated patients at first, followed by profiles in treated patients, were pooled together. Details on patient demographics, study protocol and type of data (mean or individual data) used for model development and external validation are described in Table 1 and Table 2, respectively. If information about the covariates of interest was missing, assumptions were made, including imputation, as appropriate. If body weight was not reported, a mean body weight of 70 kg was assumed for adults, while for patients younger than 18 years, reference weight values were derived from the weight charts from Disabled World.[32] Finally, if transfusion data were not reported in the original publications, assumptions on blood consumption were made on a case-by-case basis. A detailed description of all the assumptions relative to body weight or blood consumption is provided in Tables S1 and S2.

TABLE 1 Clinical studies selected for model development

Reference	Control arm	Drug	Dose (mg/kg/d)	No. subjects	Individual data	Mean age (y)
12	No	Deferiprone	78.2	12	No	15.9
15	No	Deferiprone	75	151	No	21.3
16	Yes	Deferiprone	50	30	No	4–14
			75	21		
			n/a	24		
20	No	Deferiprone	75	20	Yes	34.47
22	No	Deferiprone	75	71	Yes	20
24	No	Deferiprone	75	20	Yes	n/a
25	No	Deferiprone	From 75 to 100 in 8 wk	29	No	25.1
28	No	Deferiprone	25–50	8	Yes	n/a
13	No	Deferasirox	6.2	15	No	17
			10.2	78		
			19.4	84		
			28.2	119		
14	No	Deferasirox	From 50 to 100	609	No	30.6
				984		
				150		
17	No	Deferasirox	11.3	20	No	6.7
				20		14.1
27	No	Deferasirox	10	24	No	23.7
			20	24		25.6
18	Yes	-	-	24	Yes	6.8

n/a – not available.

TABLE 2 Clinical studies selected for external model validation

Reference	Control arm	Drug	Dose (mg/kg/d)	No. subjects	Individual data	Mean age (y)
[19]	No	Deferiprone	75–100	58	No	12
[23]	No	Deferiprone	70	29	Yes	22
[31]	No	Deferiprone	79.1	73	No	11
[21]	No	Deferasirox	20–38	119	No	19
[26]	No	Deferasirox	33.6	71	No	20.5
[29]	No	Deferasirox	23.1	237	No	13.3
[30]	No	Deferasirox	19.4	185	No	19.2

2.2 | Pharmacokinetic models

A 2-compartment pharmacokinetic model with first-order absorption and elimination was used to describe the concentration vs time profiles of deferasirox in plasma. Full details about the model development and evaluation have been previously reported by Borella *et al.*[33] Similarly, the pharmacokinetics of deferiprone was characterised by a 1-compartment model with first-order absorption, as described by Bellanti *et al.*[34] Given the lack of individual pharmacokinetic data, these models were used to simulate average steady-state drug concentrations (Css^{AV}) based on the reported dose (s) in each study. The rationale for using (Css^{AV}) as a measure of exposure is based on the mechanism of action of the two chelating agents. Reported values for steady-state concentrations were used as reference for comparison with the simulated values following administration of doses between 20 and 40 mg/kg deferasirox or 20 and 100 mg/kg deferiprone[35] (see Table S3). Such a comparison provided insight into potential discrepancies, supporting the plausibility of the simulated exposure values for subsequent use in the current analysis.

2.3 | Drug–disease model describing ferritin response in transfusion-dependent haemoglobinopathies

A drug–disease model describing ferritin response to iron chelation in chronic-transfused patients with iron overload was developed, which consists of two main components: (i) an Emax equation describing the relationship between total body iron and serum ferritin; (ii) a turnover model describing the transfusion-dependent iron production and the drug-mediated iron degradation (i.e., chelation).

Given that the plasma (or serum) ferritin concentration is known to be positively correlated with total body iron stores,[36,37] a hyperbolic (Emax) function was used to describe this relationship, taking into account the capacity-limited ferritin production when iron levels are high, as in the case of iron overload (Equation 1).

$$\mathrm{FERRITIN}(t) = \frac{Emax_{ferritin} \cdot IRON(t)}{A_{50iron} + IRON(t)} \quad (1)$$

where $Emax_{ferritin}$ is the maximum concentration value that ferritin can have under transfusion-dependent haemoglobinopathies and $A_{50\,iron}$ is the iron level (mg) that produces half of the maximum ferritin concentration. FERRITIN(t) and IRON(t) are the concentration of ferritin and iron amount at time t. This relationship also assumes a relatively fast equilibration between ferritin and plasma NTBI.

Second, an indirect response model was used to describe the iron turnover process, i.e. a zero-order production rate (K_{in}) and a first-order degradation rate (K_{out}).

$$\frac{dIRON(t)}{dt} = K_{in} - K_{out}\mathrm{IRON}(t) \quad (2)$$

The initial iron content was derived from the predicted ferritin value at baseline by reversing the relationship between ferritin and iron:

$$\mathrm{IRON}_{(t\,=\,0)} = \frac{A_{50iron} \cdot FERRITIN_{(t\,=\,0)}}{Emax_{ferritin} - FERRITIN_{(t\,=\,0)}} \quad (3)$$

where the predicted serum ferritin value at baseline ($FERRITIN_{(t=0)}$) was calculated using the serum ferritin value measured at time 0 ($FERRITIN_{t\,=\,0,measured}$) after subtraction of the measurement error:

$$\mathrm{FERRITIN}_{(t\,=\,0)} = \frac{FERRITIN_{t\,=\,0,measured}}{e^{\left(\eta_{FERRITIN_{t\,=\,0,measured}}\right)}} \quad (4)$$

where $FERRITIN_{t\,=\,0,measured}$ is the measured serum ferritin value at time 0 and $\eta_{FERRITIN_{t\,=\,0,measured}}$ is the residual error term on $FERRITIN_{t\,=\,0,measured}$, which is assumed to be normally distributed with mean 0 and variance to be estimated.

In the turnover model, iron elimination was described by an elimination rate constant (K_{out}) and parameterised as a linear function of the steady state exposure to a chelating agent (Equation 5). During model development, different concentration–effect relationships (e.g., linear model, Emax model) were tested.

$$K_{out} = f(Css^{AV}) \quad (5)$$

Physiological processes associated with iron elimination such as bleeding, sweating, and skin desquamation were considered negligible (0.5–2 mg/d) compared to the elimination resulting from drug-induced chelation. These values were assumed to be rather constant during the course of treatment and therefore not parameterised for the purposes of this analysis.

Subsequently, the effect of blood transfusions was incorporated into the model by the introduction of a positive correlation between the annual blood consumption (BLOODCONS) and the zero-order input K_{in}. Instead of a typical parameterisation based primarily on physiological iron uptake, a conversion factor of 1.16 mg/mL was applied to the annual blood consumption to describe the correlation between red blood cells and iron levels/kg body weight (i.e., 100 mL of red blood cells corresponds to 116 mg of iron per/body weight)[5]:

$$K_{in} = 1.16 \cdot \text{BLOODCONS} \quad (6)$$

Fixed and random effects were introduced in a stepwise manner. Interindividual variability (IIV) and interstudy variability (ISV) was assumed to be log-normally distributed. Model building was performed using the first-order conditional estimation method with interaction in NONMEM v.7.3 (Icon Development Solutions, USA).

Model selection was based on the decrease in the objective function values, completion of the estimation and covariance steps, precision of the parameter and error estimates, number of significant digits, correlation between parameters, and absence of zero gradients. Evaluation of the final model was based on standard diagnostic criteria, including goodness-of-fit plots, visual predictive check (VPC) and normalised predictive distribution error. Nonparametric bootstrap (1000 samples) was used to evaluate the precision of parameter estimates (standard error and confidence intervals; PsN v.4.2, Uppsala University, Sweden). To further assess model performance, VPCs were performed (500 replicates) using an external validation data set (Table 2). R v.3.0.3[38] was used for data manipulation, graphical and statistical summaries.

Using the final model and assuming a population with comparable transfusional regimens (i.e., 150 mL/kg/y), simulation scenarios were then implemented to characterise the effect of different baseline ferritin concentrations and chelating agents on the overall ferritin response. Similarly, simulation scenarios were evaluated to explore the implications of differences in chelation therapy for ferritin trajectories and iron overload.

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[39] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[40]

3 | RESULTS

3.1 | Parameterisation and model evaluation

Mean and individual serum ferritin concentration data used for model development are reported in Figure S1. A schematic representation of the final drug–disease model describing the ferritin response to iron overload is presented in Figure 1. Given the therapeutic range of doses evaluated in the available clinical studies, a linear model was deemed appropriate to describe the chelating effects, as it accurately described the observed changes in serum ferritin. This parameterisation implies a change in iron elimination rate that is proportional to the steady state concentrations of the chelating agent (i.e., $K_{out} = \text{SlopeDrug} \cdot Css^{AV}$), where different slope parameters were estimated for deferiprone and deferasirox. Nonlinear models (Emax and sigmoidal Emax models) were also tested, but the available data did not allow the estimation of additional parameters, such as potency or maximum effect. By contrast, a significant improvement in the model was observed by adding IIV on K_{in} when individual data were available. Similarly, model fitting improved following incorporation of IIV and ISV on the slope parameter describing the effect of deferiprone. The lack of individual data did not support the estimation of these stochastic components for deferasirox. A proportional error model was used to describe residual error variability. Model diagnostics, including VPC and normalised predictive distribution error results (Figures 2 and S2 to S5) confirm the model's ability to describe summary population and individual data. The final model parameters and the bootstrap results are presented in Table 3.

Lastly, model predictive performance was assessed using the external validation data set (Table 2). VPC results showed that ferritin response is adequately described by the final model following treatment with both chelating agents (Figure S6).

Considering the application of this model as a tool for treatment personalisation, a sensitivity analysis was performed to explore the potential effect of imputed missing blood consumption information on parameter estimates. The final model was re-run using a reduced data set, including only studies with explicitly reported blood consumption data. This preliminary evaluation showed that parameter estimates were similar to those obtained with the full data set; however, parameters were estimated with lower precision.

3.2 | Effect of baseline covariates and drug exposure on ferritin response

Given the complex homeostatic processes associated with iron elimination and ferritin production, simulations were performed to

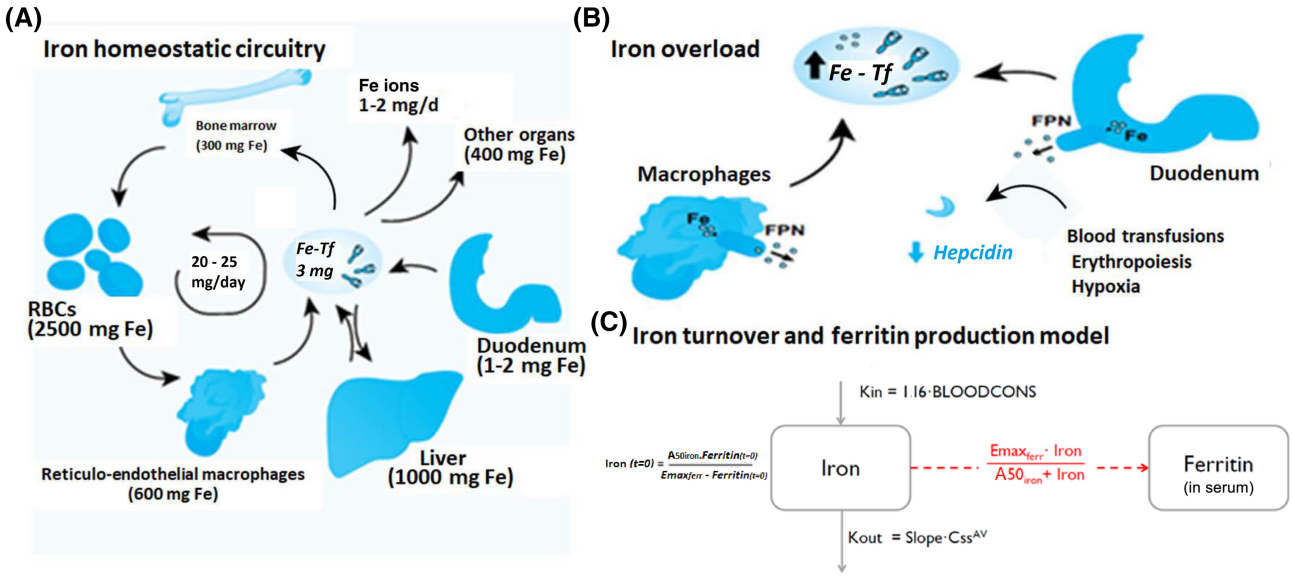

FIGURE 1 Schematic representation of the iron homeostatic circuitry and processes associated with iron overload *(Modified with permission from Ginzburg et al.[41]).* (A) Iron cycling involves transferrin-bound iron in circulation and within haemoglobin inside red blood cells. Iron recycling from senescent red blood cells in macrophages provides the largest proportion of iron available for erythropoiesis. Iron is also used for multiple proteins in other tissues. Small amounts of iron are absorbed daily to offset losses, and the liver is the site of iron storage. (B) In addition to frequent blood transfusion, iron overload also results from decreased hepcidin, which enables increased iron absorption and recycling, eventually overwhelming transferrin iron binding capacity, leading to nontransferrin-bound iron and dysfunctional parenchymal iron deposition. (C) Iron turnover and ferritin production have been parameterised into a drug–disease model describing the ferritin response in transfusion-dependent haemoglobinopathies. See main text for further details on the definition of model parameters. Fe, iron; Fe-Tf, transferrin bound iron (holo-transferrin); FPN, ferroportin; RBCs, red blood cells

describe the effect of baseline covariates and interindividual differences in drug exposure. Our analysis suggests significant differences in the time course and magnitude of changes in ferritin concentrations depending on a patient's ferritin levels at baseline and chelating agent. Assuming comparable blood consumption (150 mL/kg/y) and no dose variation during a period of 12 months (e.g., 100 mg/kg/d for deferiprone and 40 mg/kg/d for deferasirox), as shown in Figure 3, it becomes evident that the lower the ferritin concentrations at the start of the treatment, the less pronounced are the changes over time. Interestingly, at therapeutic doses and comparable blood consumption, the effect of deferasirox seems to be smaller than that achieved after administration of deferiprone (Figure 4). Our results also reveal a reduction of approximately 50% in the amount of iron stored in ferritin over the 12 months following treatment with 100 mg/kg deferiprone, while only a 20% reduction is observed for deferasirox (administered at 40 mg/kg doses; Figure 5).

Finally, the effect of different chelating agents on treatment outcome was investigated. Simulation scenarios were evaluated, including a wide dose range of deferiprone (i.e., 75, 85, 95 and 100 mg/kg/d). The results show that higher doses lead to a higher elimination rate and consequently to a lower ferritin steady state plateau (Figure S7). This evaluation was complemented by exploring the effect of increasing body weight, which is particularly important for the paediatric population (Figure S8).

4 | DISCUSSION

Despite the current understanding that iron excess results in iron accumulation in tissues and organs, there have been limited efforts to assess in a strictly quantitative manner how iron overload affects ferritin production and circulating ferritin concentrations in serum.

Here we have shown how model-based approaches can be used to characterise iron overload and ferritin response in transfusion-dependent haemoglobinopathies. Of note is the delay in ferritin response relative to the start of chelation therapy. Such a phenomenon is determined by a complex interaction between homeostatic mechanisms, zero- and first-order processes associated with blood transfusions, ferritin turnover, and drug clearance.[42]

As there are no physiological mechanisms to excrete excess iron, patients receiving regular blood transfusion will inevitably be affected by iron overload. Our analysis showed that iron accumulation from blood transfusion can be described by a zero-order process, which varies proportionally to total blood consumption (per year). By contrast, clearance of excess iron was parameterised as a first-order process. In these conditions, net iron elimination was found to increase proportionally with increasing steady state concentrations of the chelating agent.

From a clinical perspective, snapshots of this intricate interaction do not necessarily provide insight into the contribution of chelating

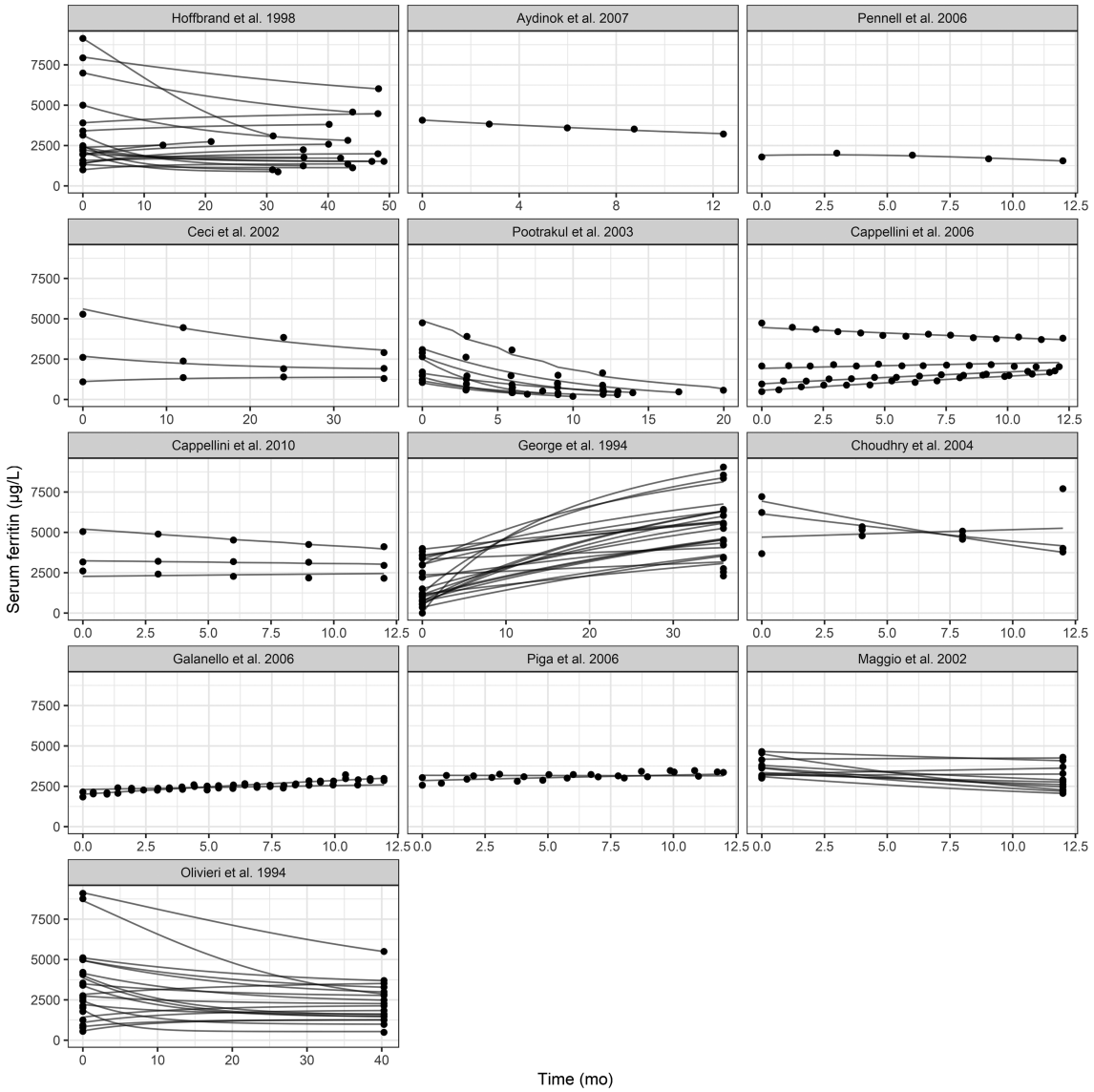

FIGURE 2 Plots of observed serum ferritin concentrations (black circles) and individual predictions (grey lines) for the final model stratified by study

TABLE 3 Parameter estimates of the final model

Parameter	Unit	Population estimate (%RSE)	Bootstrap median (90%CI)
$Emax_{ferritin}$	mg/mL	11.7 (10%)	12.2 (10.0–32.0)
$A_{50\ iron}$	mg	1240 (14%)	1293 (956–5082)
SlopeDrug(deferiprone)	L/(mg mo)	0.0109 (14%)	0.0107 (0.0079–0.0131)
SlopeDrug (deferasirox)	L/(mg mo)	0.0013 (12%)	0.0012 (0.0008–0.0018)
IIV on ***SlopeDrug*** (deferiprone)[a]	-	0.109 (53%)	0.100 (0.021–0.221)
ISV on ***SlopeDrug*** (deferiprone)[c]	-	0.437 (145%)	0.441 (0.306–0.639)
IIV on ***BASELINE***[a]	-	0.322 (4%)	0.319 (0.212–0.408)
IIV on ***BLOODCONS***[a]	-	0.462 (21%)	0.398 (0.188–0.762)
σ_{PROP}[b]	-	0.00978 (4%)	0.0092 (0.0058–0.0148)

IIV: interindividual variability; ISV: interstudy variability; RSE: residual standard error; CI: confidence interval.
[a]Reported as OMEGA(), as in the NONMEM output for IIV.
[b]Reported as SIGMA(), as in the NONMEM output for the variance of the residual error.
[c]Reported as OMEGA(), as in the NONMEM output for ISV.

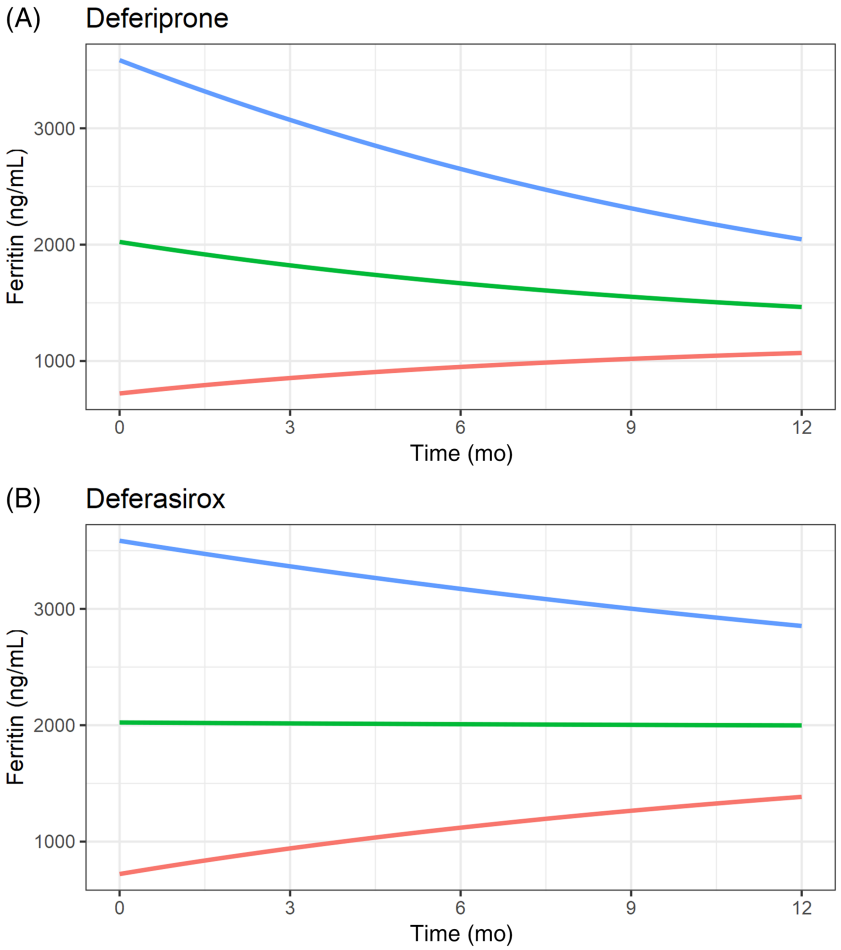

FIGURE 3 Predicted time course of serum ferritin following administration of deferiprone (A) and deferasirox (B) in patients with different ferritin concentrations at the start of the treatment: high baseline ferritin level (≥3500 ng/mL, blue line), median baseline ferritin level (≥2500 to <3500 ng/mL, green line) and low baseline ferritin level (<2500 ng/mL, red line), assuming comparable blood consumption (150 mL/kg/y) and no dose variation during the period of investigation (i.e., 100 mg/kg/d for deferiprone and 40 mg/kg/d for deferasirox)

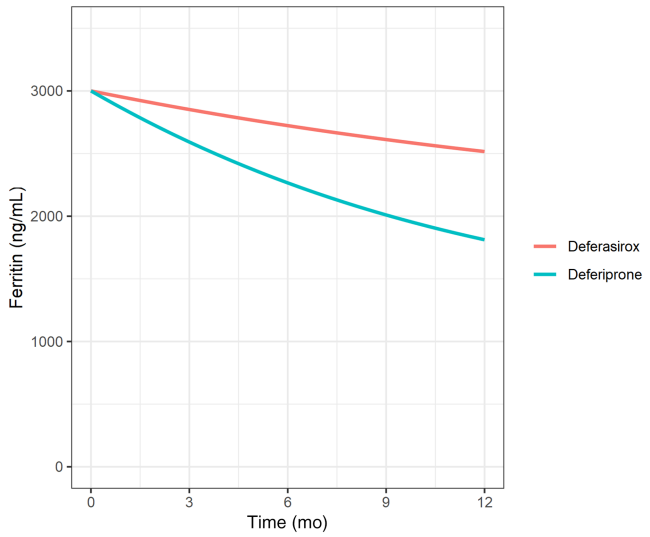

FIGURE 4 Predicted reduction in serum ferritin concentrations over 12 months following administration of 100 mg/kg/d deferiprone (light-blue line) and 40 mg/kg/d deferasirox (red line), assuming comparable blood consumption (150 mL/kg/y) and ferritin baseline concentrations of 3000 ng/mL

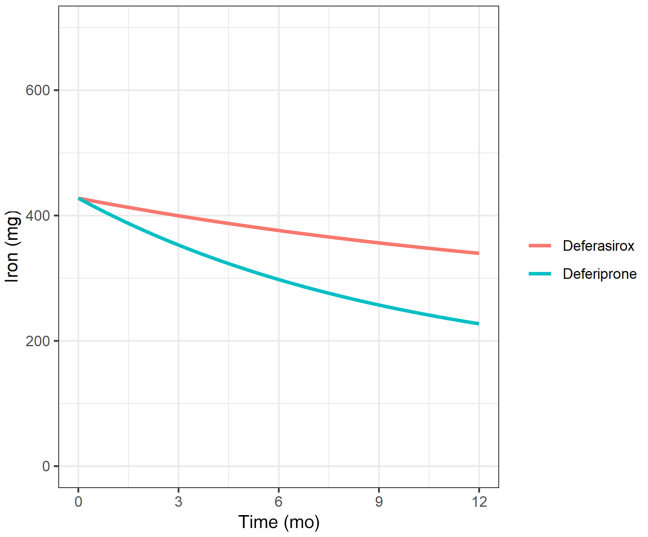

FIGURE 5 Predicted reduction in iron overload over 12 months following administration of 100 mg/kg/d deferiprone (light-blue line) and 40 mg/kg/d deferasirox (red line), assuming comparable blood consumption (150 mL/kg/y) and same iron overload at baseline (i.e., approximately 400 mg)

agents to iron removal or the downstream effects on the biomarker of interest (i.e., ferritin). In fact, monitoring of treatment response based on serum ferritin concentrations remains empirical. A decrease in biomarker levels is considered good evidence of a reduction in body iron burden but the absence of such a trend does not exclude lower iron overload. Hence, clinicians still face uncertainty in assessing whether the lack of a drop in serum ferritin with chelation indicates that the patient is a *nonresponder*, and a different dose should be considered or whether results are due to a delay relative to the start of treatment, and consequently, the chelation regimen is appropriate.

Clearly, there have been gaps in the way changes in ferritin are described and how such changes correlate with iron clearance.[43] This is partly due to the fact that only a very small fraction of body iron is available for chelation at any moment of time. As iron chelators interact with low molecular weight *labile* iron pools better than with iron stored as ferritin or haemosiderin and labile iron is constantly being generated, chelation efficiency increases when a chelator is available at all times.[5] Our approach has allowed us to establish the relationship between iron concentration, ferritin production and circulating serum ferritin, providing the basis for a parameterisation that describes how variation in iron exposure correlates with chelation-induced iron clearance.

To our knowledge this is the first time a drug–disease model has been developed for iron overload with direct application for the evaluation of ferritin response in patients undergoing chelation therapy with deferiprone or deferasirox. Our results also highlight the impact of disease- and patient-specific factors, such as the annual blood consumption and the serum ferritin baseline at the start of the treatment, which determines the trends and most likely trajectory of serum ferritin following chelation therapy. Moreover, our analysis reveals that despite similar mechanisms of chelation, there are significant differences in the potency of the two drugs. It appears that at therapeutically recommended doses, higher iron clearance and larger reduction in ferritin concentrations are achieved after administration of deferiprone. For example, simulations suggest that for a patient with a baseline ferritin of 3000 ng/mL, ferritin target levels of 2000 ng/mL are reached within 9 months after initiation of treatment with deferiprone, whilst the same level is not reached even at 12 months for deferasirox. These results are in agreement with previous findings reported by Pepe *et al*.,[44] who showed that deferasirox monotherapy is less effective than deferiprone in reducing iron overload in critical organs. Moreover, a recent meta-analysis based on 16 studies suggested that deferiprone was more efficacious in reducing myocardial iron content compared to deferasirox or deferoxamine.[45] Lastly, in a consensus statement of the American Heart Association, it has been reported that evidence from well-conducted randomised controlled trials showed superior efficacy of deferiprone compared to versus deferasirox when compared to deferoxamine standard treatment.[46]

Whereas significant interindividual differences exist in the time course of serum ferritin concentrations relative to the start of chelation therapy, it is striking that so little has happened to date to establish how baseline characteristics, transfusion blood volume and chelation determines such differences.[7,47] Similar approaches have been developed successfully in other therapeutic areas.[48–54] For instance, compartmental models have been developed for antidiabetic drugs where the delay in response and impact of disease progression were characterised and subsequently used to assess the need to adjust therapy in Type 2 diabetes mellitus (T2DM).[50] More recently, an integrated glucose-insulin model was successfully applied to evaluate the differences between T2DM patients across a wide range of glycaemic control. The analysis showed how IIV in baseline fasting serum insulin, fasting plasma glucose, and glycated haemoglobin correlate with insulin sensitivity, β-cell function and disease progression in the target population.[49,51] Indirect response models have been successfully applied to describe the delay in low-density lipoprotein lowering effects relative to statin plasma concentrations, which was used to quantitatively assess the effects of ezetimibe, a cholesterol absorption inhibitor, and baseline low-density lipoprotein–cholesterol concentrations on the success rate of rosuvastatin therapy.[52] Similarly, an indirect response model with inhibition of C-reactive protein as input was used to describe the concentration–effect relationship between adalimumab concentration and C-reactive protein concentration in patients with rheumatoid arthritis. Simulations with this model showed that the current dosing regimen for adalimumab results in a long delay to maximal effect, suggesting that the use of a loading dose could decrease this delay.[53]

4.1 | Applications and future perspectives

An immediate application of this model is its use as a predictive tool. There are numerous clinical questions which have not yet been adequately addressed. For example, simulations can be performed to assess the effect of different covariates distributions (e.g., high or low blood consumption, different severity of iron overload) on the ferritin response. It can also provide insight into iron balance, i.e., it can describe how iron levels (mg) vary in the iron turnover compartment along with the changes in serum ferritin. Moreover, it offers a basis for the evaluation of alternative trial designs (e.g., titration algorithms, total trial duration, inclusion and exclusion criteria). Another important therapeutic application is the possibility to explore changes in the dosing interval of deferiprone. Further refinement of the model may provide evidence of treatment performance for a twice daily regimen, as compared to the currently recommended 3 times daily doses. Such an evaluation would also shed light on the observed differences in ferritin response between the two chelators.

4.2 | Limitations

We acknowledge that the use of limited published data and the semimechanistic nature of the model may not be sufficient to describe the full homeostatic circuitry at physiological levels or during iron overload, as the one reported by Salgado *et al*.,[7] which may have limited application in clinical practice. By contrast, the parameterisation proposed here provides insight into clinically

relevant aspects of iron homeostasis in the presence of chelating agents.

The lack of individual pharmacokinetic and pharmacodynamic data for all the studies included in the analysis also impaired our ability to distinguish sources of variability and obtain precise estimates of covariate effects for individual patients. In addition, the unavailability of a full dose-exposure–response also limited the structural model selection, as only therapeutic doses have been tested in the published clinical trials.[27–29,54–55]

Despite such a limitation, the available data enabled us to identify and quantify the contribution of factors that were not only statistically significant, but also biologically plausible. As such, we believe that more precise parameter estimates may be obtained when individual patient data from efficacy trials become available.

Consequently, the use of a typical Emax model was not appropriate and the effect of chelation on iron elimination was modelled as a linear function of steady state concentrations. Another important point to consider is compliance and treatment adherence, which may often be overlooked in long-term clinical trials. Poor or variable adherence to treatment is known to occur in clinical practice for chronic conditions such as thalassemia and sickle cell disease.[56] Our analysis has been performed under the assumption that variable adherence was not a contributing factor to interindividual differences in serum ferritin concentrations over the course of treatment. Rather, we have assumed that these were primarily determined by differences in iron clearance and chelator exposure.

In summary, the development of a drug–disease model describing ferritin response to iron chelation in patients affected by iron overload allowed us to characterise the relationship between blood consumption, iron overload and ferritin response in a semimechanistic manner. Moreover, this preliminary analysis indicates that individual differences in baseline serum ferritin concentrations play an important role in the overall response to iron chelators. Given the choice of parameterisation, this model allows assessment of the dosing requirements for personalised treatment of patients with transfusion-dependent haemoglobinopathies.

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COMPETING INTERESTS

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CONTRIBUTORS

E.B., S.O., P.M. and O.D.P. contributed to the planning and development of the modelling strategy and data analysis plan. E.B. and S.O. performed the data analysis. E.B., S.O., P.M. and O.D.P. contributed to the writing of the manuscript.

DATA AVAILABILITY STATEMENT

The data used for the purposes of this investigation have been retrieved from the list of publications in Tables 1 and 2.

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SUPPORTING INFORMATION

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