From data to models : reducing uncertainty in benefit risk assessment : application to chronic iron overload in children

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CHAPTER 8

Model-based characterisation of the acute and long-term unfavourable effects of iron chelation therapy

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Ready for submission

Summary

Aims: The evaluation of the safety profile during the development of a drug is a challenging undertaking, especially as the drug-specific adverse events may be intertwined with disease-related complications. Using iron chelation therapy as an example, we propose a model-based approach to integrate epidemiological and pharmacological data for the characterisation of the acute, long-term adverse events and the disease complications due to transfusion-dependent iron overload.

Methods: Longitudinal data from a reference group of patients (n= 27) affected by β-thalassaemia major under chelation therapy with deferoxamine were evaluated in conjunction with literature data on the short-term safety profile of deferoxamine. Occurrence of the secondary co-morbidities hypothyroidism and diabetes mellitus was analysed based on a time to event approach in NONMEM v.7.2.0. In this analysis historical data were included as priors to reduce uncertainty in parameter estimates. Occurrence of the acute drug-specific adverse events arthralgia/myalgia and anaphylaxis were modelled as dose-dependent and dose-independent events.

Results: The predicted incidence for hypothyroidism and diabetes based on the hazard models with mean (90% CI) was 6.3% (0-14.8) and 8.9% (0-18.5), respectively. For a 45 mg/kg/day dose the mean (95% CI of the mean) simulated incidences for anaphylaxis and arthralgia/myalgia were 0.154% (0.139-0.169) and 21.01% (20.85-21.17) respectively; other doses as well as different compliance patterns were evaluated both for drug-specific AEs and disease complications.

Conclusions: A model-based approach provides the basis for a structured evaluation of the safety profile of drugs at different stages of development and for risk management, allowing integration of clinical and epidemiological data and consequently discrimination between the disease-related and the drug-related adverse events. Our simulations show that both chelation and transfusion history play a major role in determining the long-term adverse events and complications of disease. The findings also reveal a delicate balance between acute and long-term complications, indicating that inadequate chelation therapy or poor compliance can affect the desired therapeutic goal.

8.1 Introduction

In many chronic paediatric diseases such as transfusion-dependent haemoglobinopathies, where life-long red blood cell (RBC) transfusion is essential to survive (1–7), the direct and instantaneous therapeutic effectiveness needs to be balanced with long-term complications that depend both on the treatment intervention and the underlying disease progression. Two major aspects need to be considered when evaluating long-term effects: the disease progresses over time and may lead to disease specific complications and at the same time the frequency of drug-specific AEs may change over time or delayed, time-dependent AEs may be occur (8,9). Furthermore, in contrast to drug efficacy, even the short-term evaluation of drug-specific AEs can be extremely challenging, as data are often not available (e.g., a given event might not be observed during a clinical trial, especially if the incidence is relatively low) or not quantifiable due to recognised methodological issues (10–12). The two aspects very often overlap, making it rather difficult to discriminate the underlying cause. Lack of understanding of such an interaction may lead to inaccurate assessment of the safety profile of a drug. In fact, to fully characterise the safety profile, a variety of endpoints need to be considered in parallel, taking into account the correlations among them.

Chronic iron overload

Even though the management of the chronic RBC transfusion regimen and the availability of adequate iron chelation therapy have improved significantly in the last decades, patients with β-thalassemia will still experience a number of complications throughout their entire life (6,13,14).

Among the disease related complications, iron overload is the most clinically relevant and it is associated with several co-morbidities such as cardiac dysfunction, liver fibrosis, hypogonadism, hypothyroidism, hypoparathyroidism and diabetes mellitus (6,13,14). Cardiac disease caused by myocardial siderosis is the most relevant one, causing death in 71% of the patient population (15).

In the absence of an innate mechanism to remove the excess of iron, treatment with iron chelators is vital to prevent its accumulation and to manage the related complications (16–19). In addition to the disease related complications, the therapeutic intervention itself may also cause a number of undesired events (different for each iron chelator available on the market) that will play an essential role in the ability of the patient population not only to accept the intervention (poor adherence) but also to coexist with these complications for a life-long term. In this analysis we focus on the iron chelating agent deferoxamine (DFO), that is first-line therapy for transfusion-dependent diseases and has been available for the treatment of iron overload for more than 35 years (2,6,16–21). Among the various limitations of deferoxamine therapy recognised by clinicians and experts in the field

(6,17,19,22), compliance to the treatment plays a crucial role in the overall effectiveness of the treatment as well as the related complications.

Using DFO for the treatment of iron overload as an illustrative example, we propose and evaluate the advantages of a model-based approach for the characterisation of the safety profile of a medicinal product. We also show how modelling allows integration of epidemiological (literature) and pharmacological data for the quantification of the acute (drug specific) and long-term (disease specific) AEs of iron chelation therapy. Lastly, we show how the effect of treatment compliance can be assessed and correlated to acute and long-term events, disentangling the impact of inadequate chelation therapy from variable pattern of treatment compliance.

8.2 Methods

Data

To evaluate the model-based approach in the context of chronic iron overload we decided to select data in thalassaemic patients undergoing single therapy with deferoxamine and specifically collected data on incidence of hypothyroidism and diabetes mellitus. The choice of these two co-morbidities was made because they both are a clear consequence of the disease and no other influence of the drug therapy is expected except for the prevention of the complication itself. Furthermore, in the absence of clinical data on drug-specific AEs we simulated incidences for two extreme cases (i.e., arthralgia/myalgia as a very common AE and anaphylaxis as a rare AE) to assess their profiles after short- and long-term treatment. Specific details on the data are provided in the next few paragraphs.

Clinical Data on hypothyroidism and diabetes mellitus

The modelling analysis was performed using retrospective clinical data in 27 patients with β thalassaemia major from three different Italian centres: A.O. Universitaria Consorziale Policlinico di Bari U.O. Pediatria Federico Vecchio; A.O. Universitaria Policlinico di Sassari Clinica Pediatrica, ASL 1 D.H. per Talassemia; A.O. di Padova Clinica di Oncoematologia Pediatrica. The study has been conducted in full conformance with the principles of the Declaration of Helsinki and with the local laws and regulations concerning clinical trials. The protocol and the informed consent documents have been formally approved by the relevant research ethics committee of each clinical site.

Clinical data were collected retrospectively for a maximum of ten years in 27 patients affected by transfusion-dependent diseases, receiving deferoxamine as single drug for iron chelation therapy. Baseline characteristics of the patient population are provided in Table 1. Patients contributed with 40.2 observations on average (sd: 17), with a minimum of 4 samples per year.

Table 1. Baseline characteristics of the patient population (n=27)

	Units	Median	Range
Age	Years	14.6	6.8-19.9
Weight	Kg	46	17.5-71
Height	Cm	154	111-173
TSH	mIU/L	2.34	0.58-83.2
FT4	ng/dL	1.05	0.73-1.43
AST	U/L	33	7-159
ALT	U/L	56	9-372
Glucose	mg/dL	91	52-444
Creatinine	mg/dL	0.6	0.2-1.12
Ejection Fraction	%	64	35-77
Ferritin	μg/L	2260	393-8500

Literature data on co-morbidities and drug specific AEs (data abstraction)

A literature search has been performed to retrieve data on the incidence of hypothyroidism and diabetes mellitus in the thalassemic population. At first reports from the Central Bureau of Statistics, The Netherlands were used as reference for the background incidence of the two co-morbidities in the overall population (23). Subsequently, a comprehensive literature search was performed using MESH terms in PubMED, in which articles describing hypothyroidism and diabetes in thalassaemic patients were retrieved. Thirteen articles in total (15,24–32,32–34) were identified with relevant information on the incidence of both co-morbidities. The keywords used comprised the names of the co-morbidity in combination with β-thalassaemia major, transfusional iron overload, deferoxamine, and a combination of them. In parallel, a separate search was performed on publications showing supporting evidence for the use of serum ferritin levels as a predictor for the occurrence of the two co-morbidities in thalassaemic patients (35–39). Of relevance is the finding that co-morbidity is with higher incidence in patients whose serum ferritin levels are consistently above 2500 μg/L (35–39). This threshold represents the boundaries for a shift in iron overload from moderate to a severe state (2,6,40–42). Given the level of detail provided by the authors, we have focused on the work by Belhoul et al. who demonstrated in a group of almost 400 patients a clear distinction in the incidence of hypothyroidism and diabetes mellitus in relation to a serum ferritin threshold of 2500 μg/L (38).

Finally for the evaluation of drug specific adverse events (anaphylaxis and arthralgia/myalgia), estimates reported on the summary of product characteristics (SPC) of DFO (20) were used to simulate the events of interest. The pharmacological classification proposed by Wills and Brown was used to select drug specific adverse events based on their frequency, time of onset and the relation with dose (43). Arthralgia/myalgia was selected as

an example of a very common Type A (dose-dependent) AE with a frequency greater than 1/10. In addition, anaphylaxis was identified as a rare, Type B (dose-independent) AE with a frequency between 1/10000 and 1/1000.

Modelling

Hazard models for hypothyroidism and diabetes mellitus

The models for hypothyroidism and diabetes were developed based on the combination of literature and clinical data. Three steps were taken for the development of each model:

1) An exponential hazard model was built based on literature data on the incidence of the co-morbidity in thalassaemic patients (disease effect) and in a healthy population (baseline);
2) The estimated parameters were used as priors to estimate the hazard in the retrospective clinical data in thalassaemic patients;
3) Literature data were used to incorporate the effect of serum ferritin levels as a covariate on the final hazard model.

During step 1, a time to event analysis was performed for both hypothyroidism and diabetes by implementing an exponential hazard model in NONMEM v.7.2 (Icon Development Solutions, USA). The initial model was based on the epidemiology reports and literature data and consisted in the following relationship between hazard and survival:

$$S(t) = e^{-\int_0^t h(t)dt} \qquad \text{Equation 1}$$

Where the hazard is h(t), and the survival (S) is a function of the cumulative hazard within the time interval 0 to t. The effect of disease was included as a covariate function (λdis) that would modify the background (initial) hazard (h_0) as follows:

$$h(t) = h_0(t) * e^{\lambda dis} \qquad \text{Equation 2}$$

In step 2 the normal-inverse Wishart prior (NWPRI) option was used in NONMEM (44) to estimate the incidence of the co-morbidities in the data collected during the retrospective study in thalassaemic patients. In the presence of extremely sparse data the use of prior information was deemed pivotal to ensure unbiased estimate of the disease effect and to stabilise the model.

Finally, in step 3 the work by Belhoul et al. (38) was used to justify the inclusion of serum ferritin levels as a covariate factor in the model developed in step 2. The objective was to

demonstrate that ferritin can be considered as a predictive factor for the probability (hazard) of developing co-morbidity. The threshold of 2500 µg/L was used as reference value to dichotomise the data into two groups and ratio of the incidence of the co-morbidity in these groups was used to define the corresponding ratio in the hazard model. As shown in equation 2, the effect of the disease was described by two components depending on whether serum ferritin levels were above (λfrth) or below (λfrtl) the selected threshold:

$$h(t) = h_0(t) * e^{\lambda frth + \lambda frtl} \qquad \text{Equation 3}$$

A summary of the model building steps and parameter estimates for the hazard models of deferoxamine for hypothyroidism and diabetes mellitus is provided in Table 3.

Table 3. Model building steps and parameter estimates of the hazard model of deferoxamine for hypothyroidism and diabetes mellitus.

Hypothyroidism		
Parameter	**Description**	**Estimate**
Step 1: based on epidemiological and literature data		
$\mathbf{h_0}$	Baseline hazard	0.000496
$\boldsymbol{\lambda_{dis}}$	Disease as a predictor	2.69
Step 2: based on retrospective clinical data (step 1 used as prior)		
$\mathbf{h_0}$	Baseline hazard	0.000496 (FIX)
$\boldsymbol{\lambda_{dis}}$	Disease as a predictor	1.86
Step 3: based literature data (38)		
$\mathbf{h_0}$	Baseline hazard	0.000496 (FIX)
$\boldsymbol{\lambda_{frtl}}$	Disease when ferritin is below 2500 µg/L	1.03
$\boldsymbol{\lambda_{frth}}$	Disease when ferritin is above 2500 µg/L	2.58
Diabetes mellitus		
Parameter	**Description**	**Estimate**
Step 1: based on epidemiological and literature data		
$\mathbf{h_0}$	Baseline hazard	0.00036
$\boldsymbol{\lambda_{dis}}$	Disease as a predictor	2.72
Step 2: based on retrospective clinical data (step 1 used as prior)		
$\mathbf{h_0}$	Baseline hazard	0.00036 (FIX)
$\boldsymbol{\lambda_{dis}}$	Disease as a predictor	2.54
Step 3: based literature data (38)		
$\mathbf{h_0}$	Baseline hazard	0.00036 (FIX)
$\boldsymbol{\lambda_{frtl}}$	Disease when ferritin is below 2500 µg/L	1.56
$\boldsymbol{\lambda_{frth}}$	Disease when ferritin is above 2500 µg/L	3.33

Logistic models of acute drug specific adverse events

In contrast to the data fitting procedures used to describe the incidence of co-morbidiies, drug-specific adverse events were evaluated by simulations using the information reported on the SPC of deferoxamine.

Two approaches were used to simulate the incidence of a very common dose-dependent AE (arthralgia/myalgia) and a rare dose-independent AE (anaphylaxis). In the first case, a logistic model with non-linear regression was developed correlating the drug levels a steady-state with the probability of adverse events in an exposure-dependent manner. Steady-state concentrations were simulated based on a PK model, which is described in later in this section. The logistic model was implemented as follows:

$$P = \frac{Css^{\gamma}}{(PC_{50}{}^{\gamma} + Css^{\gamma})} \qquad \text{Equation 4}$$

where Css is the deferoxamine steady state concentration, PC_{50} is the concentration corresponding to a 50% probability of experiencing the AE, and γ is the coefficient defining the shape of the relationship. Parameter values for PC_{50} and γ were fixed to 13 ug/ml and 2.5, respectively, to ensure that simulated incidence levels correspond to the figures reported in the SPC.

In the second case, a truncated normal distribution (with x > 0) was used in R to simulate a rare, dose-independent AE (anaphylaxis). The rnorm function (45) with mean equal to 0.5 and standard deviation equal to 0.5 was used to generate the probabilities of experiencing the adverse event. A severity of grade 2-3 was assumed for all AEs. However, for the purposes of this analysis no distinction was made between severity levels at the time of the event. Data was therefore summarised only as the overall frequency of AE.

Role of compliance

In a previous investigation we have highlighted the importance of treatment compliance for the effectiveness of drug therapy in patients with chronic iron overload [Chapter 7 of this thesis]. Poor adherence was found to have a major influence on the pharmacokinetics of the drug and subsequently on the desired clinical response. Compliance to treatment will therefore be one of the factors to be evaluated in the proposed simulation scenarios in order to assess its impact on the short- and long-term complications of iron chelation therapy.

Evaluation scenarios: clinical trial and not-in-trial Simulations

Simulations were performed to investigate the impact of different dose levels yielding to a range of exposure levels and various compliance scenarios on the onset and incidence of short and long-term unfavourable effects of iron chelation therapy (46). Data were

simulated for an overall period of maximum 10 years, where the 1st year is representative of a standard clinical trial and the subsequent years reflect a follow-up interval that has the objective of capturing real life conditions that may occur over a long-term period. Simulations were performed on a hypothetical patient population with similar demographic characteristics as the patients included in the retrospective clinical study (N=27) and were based on the models and final parameter estimates described above. Doses were adjusted according to changes in body weight at the scheduled visits. To ensure that uncertainty and variability in parameter estimates are accounted for, 250 simulations were performed for each individual in each of the scenarios described below. To facilitate visual representation of the simulated data, co-morbidity data were stratified by age in two major groups: above and below 12 years of age.

Simulation of drug concentrations and serum ferritin levels

A PK model and a PKPD model previously developed by our group [Chapter 7 of this thesis] were used to simulate deferoxamine exposure and serum ferritin levels. Deferoxamine concentrations (Css) were simulated based on a two compartment pharmacokinetic model with zero-order absorption and first-order elimination. Five dosing regimens (30, 40, 45, 50 and 60 mg/kg/day for 5 days a week) were evaluated and used as input for the logistic model (evaluation of short-term effects). These data were also used for the prediction of serum ferritin profiles, as described by the PKPD model. The predicted ferritin levels were incorporated as a covariate factor in the hazard models to evaluate the long-term complications of chelation therapy.

Clinical / Experimental conditions

To ensure the availability of clinically relevant scenarios, different deferoxamine dosing regimens yielding to a range of exposure levels were tested on patients starting at three different baselines ferritin levels, namely 1500, 2500 and 3500 μg/L serum ferritin. This allowed further exploration of the correlation between ferritin levels and differences in compliance pattern. The three groups reflect well-defined populations of patients with poor chelation history (baseline at 3500 μg/L), patients with good chelation history (baseline at 1500 μg/L) and patients with unknown chelation history (baseline around 2500 μg/L).

In the initial set of simulations, exposure to deferoxamine was assumed to be constant over the course of treatment. In addition, it was assumed that all patients received the same dosing regimen: 45 mg/kg/day deferoxamine for 5 days a week. Treatment was maintained at constant dose levels for up to 10 years, under assumption of adequate or satisfactory response over time, even in those subjects showing initial ferritin levels above 3500 μg/L. Our main interest was to show how simulations can be used prospectively to evaluate long-term complications. Moreover, we demonstrate how these scenarios can be used to explore

the impact of variable treatment compliance. The selected scenarios are presented in Table 2.

Table 2. Simulation scenarios for the evaluation of different patterns of compliance.

		Number of missed doses in the stratification period				
		Single doses (Random)	**Consecutive doses (Drug holidays)**			
		Stratification				
	% of missed doses	**1 year**	**1 year**	**6 months**	**2 months**	**1 month**
Scenario 1	10%	25	25	/	5	/
Scenario 2	20%	50	50	25	10	5
Scenario 3	30%	75	75	/	15	/
Scenario 4	40%	100	100	50	20	10
Scenario 5	50%	125	125	/	25	/
Scenario 6	60%	150	150	75	30	15
Scenario 7	70%	175	175	/	35	/
Scenario 8	80%	200	200	100	40	20
Scenario 9	90%	225	225	/	45	/

Full adherence is equivalent to 250 doses per year

All the analyses described in the aforementioned paragraphs were peformed in NONMEM version 7.2 (Icon Development Solutions, USA), with exception of the rare dose-independent AE, which was performed in R. All data manipulation, graphical and statistical summaries were performed in R (v.2.14.0).

8.3 Results

Hazard models for hypothyroidism and diabetes mellitus

Two survival models (exponential hazard) were developed for the quantification of hypothyroidism and diabetes in thalassaemic patients and used for prospective evaluation through model simulations. Figure 1 shows the predictions for hypothyroidism and diabetes, as compared to the available epidemiological and literature data, as described previously in step 1. Both models show good agreement with the observed data.

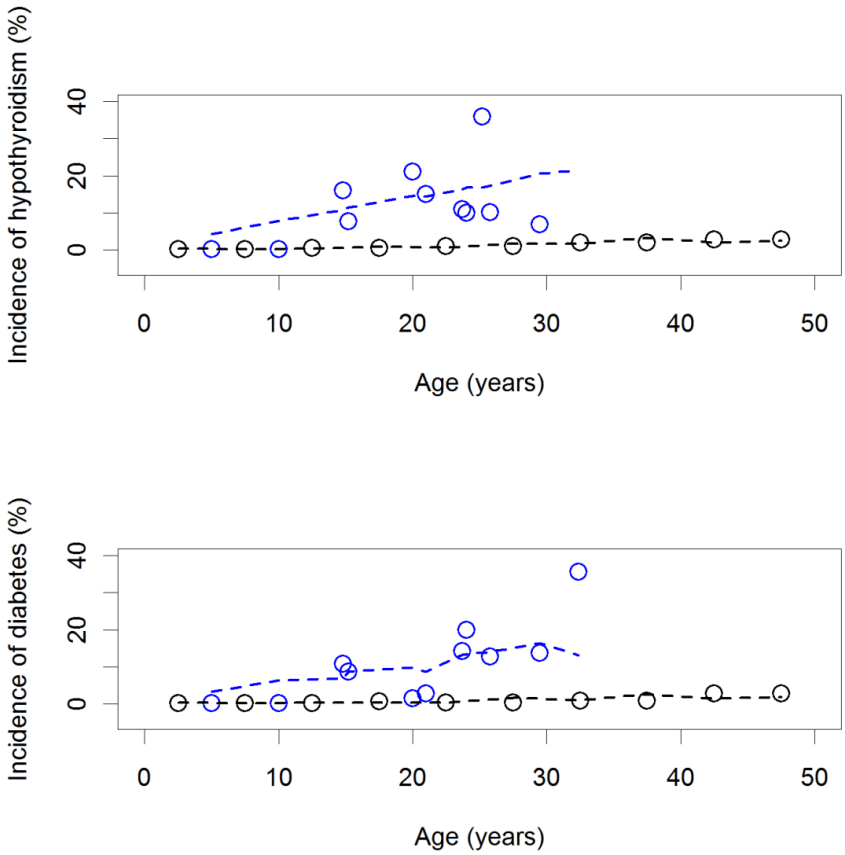

Figure 1. Performance of the hazard model for hypothyroidism (top panel) and diabetes (bottom panel) based on modelling of historical data. Black circles represent observed literature data for baseline incidence of the co-morbidities in the overall population whereas blue circles represent the observed literature incidence for thalassaemic patients. The dashed lines show model predictions in blue with respect to the patient population and in black with respect to the baseline incidence.

The results of the final model are presented in Figure 2, (after step 3: inclusion of serum ferritin as a predictor of the co-morbidity), in which published literature (15,24,32,38,39,47) data was included as prior for the analysis of the available clinical data. The mean (90% CI) predicted incidence of hypothyroidism and diabetes was 6.3% (0-14.8) and 8.9% (0-18.5), respectively. Both models were considered adequate for simulation purposes.

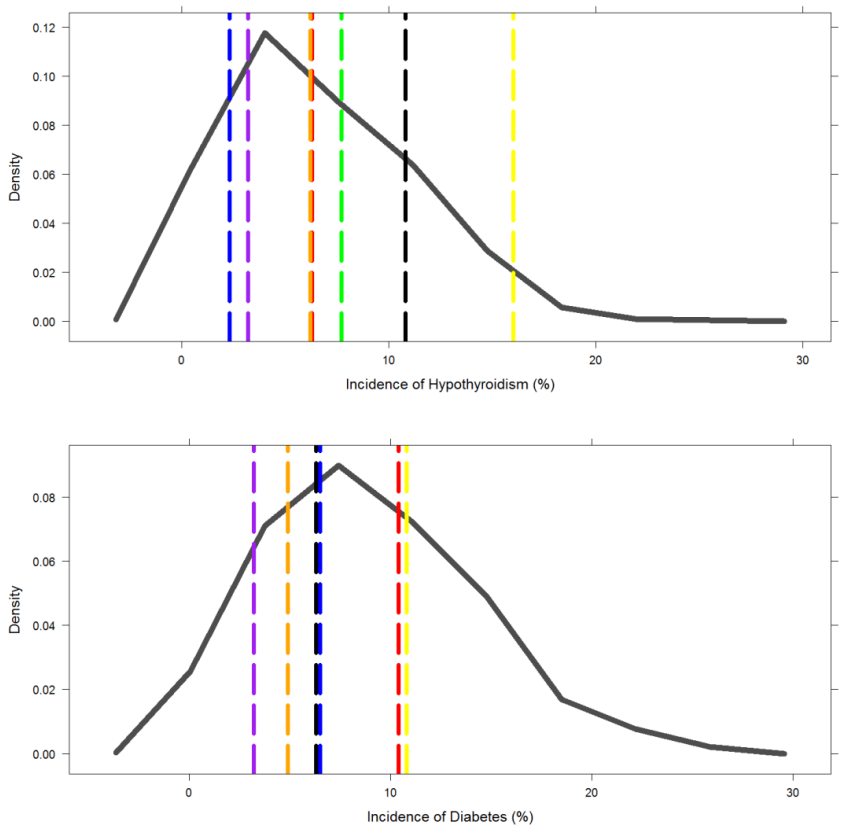

Figure 2. Validation of the hazard models for hypothyroidism (top panel) and diabetes (bottom panel). Model predicted incidence (solid dark grey line) is compared to literature data (coloured dashed lines): Borgna-Pignatti et al (black); Belhoul et al (red); Mehrvar et al (blue); Aydinoc et al (yellow); Shamshirsaz et al (green); and Kyriakou et al (orange and purple).

Clinical trial and not-in-trial simulations

The results of the evaluation of drug and treatment compliance levels on long term disease progression are presented in Figure 3. Simulation of the incidence of hypothyroidism and diabetes in a virtual population of 27 patients are stratified by age groups (below or above 12 years of age at start of treatment). In patients below 12 years of age a slight negative trend is observed indicating a reduction in the incidence of the co-morbidities with increasing dose levels; this is not the case in the other group where no significant changes are observed. Furthermore, a clear distinction in the incidence of both co-morbidities was observed for patients with different starting baseline ferritin levels. This finding highlights the relevance of transfusion and chelation history for these outcomes.

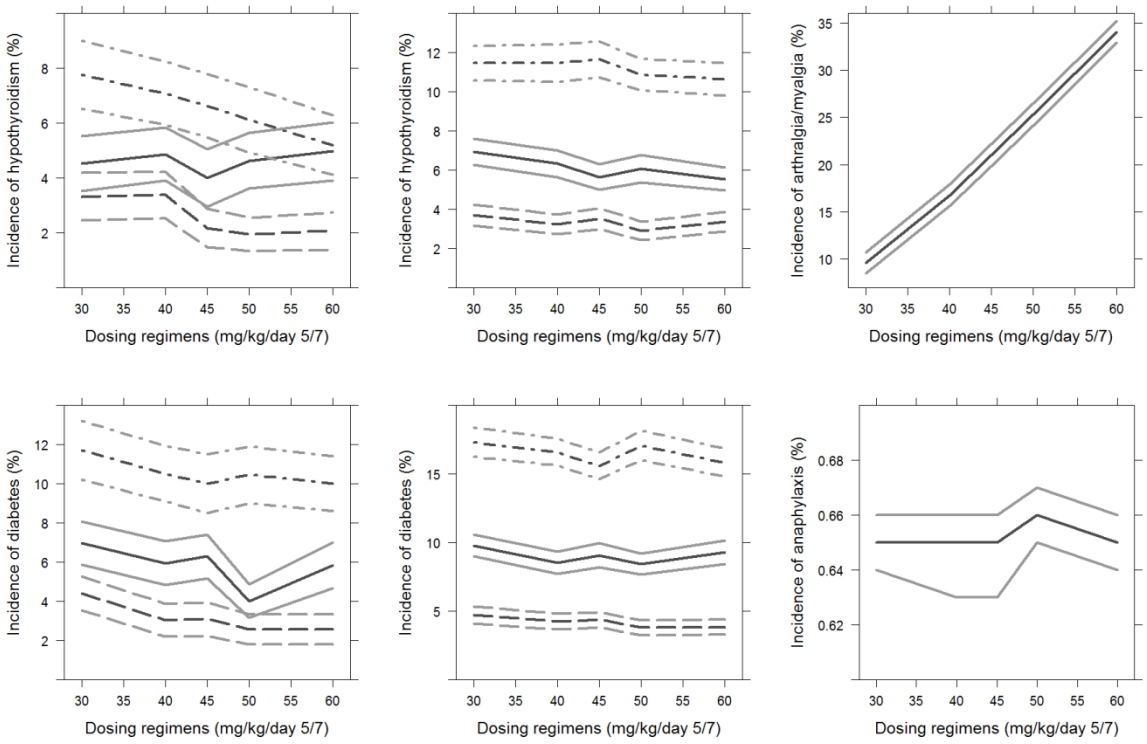

Figure 3. Effect of different exposure levels (*x axes* show different dosing regimens investigated in the simulation) on hypothyroidism, diabetes, arthralgia/myalgia and anaphylaxis in the population under investigation for an observational period of maximum 10 years. *Top left and top mid panels* show the simulations outcome for hypothyroidism after stratification of the patients into two age categories, i.e., below and above 12 years of age, respectively. *Bottom left and bottom mid panels* show the simulations outcome for diabetes in patients below and above 12 years of age, respectively. The dashed, solid and dotted-dashed lines represent respectively the three subgroups of patients with adequate, unknown and poor chelation history. The top right panel show the results for arthralgia/myalgia, whereas the bottom right panel gives the results for anaphylaxis. In all scenarios the dark grey lines represent the mean and the light grey lines represent the 95% confidence interval of the mean.

On the other hand, the simulations describing the occurrence of acute, drug-specific AEs the show the implications of dose-dependent and dose-independent adverse events, on the individual safety profile of each patient, with the incidence of myalgia/arthralgia increasing proportionally with the dose of deferoxamine.

Given the interaction between treatment response, as determined by ferritin levels and adherence to the prescribed dosing regimen, we also included an evaluation of the impact of different compliance patterns. Results are shown in Figures 4, 5 and 6 for hypothyroidism, diabetes and arthralgia/myalgia and anaphylaxis, respectively. Similarly to what we have observed when evaluating the implications of different exposure levels, stratification of the

data by age indicates an increase in the incidence of hypothyroidism and diabetes with decreasing levels of adherence in patients below 12 years of age (Figures 4 and 5 – left panels). Similar trends are observed among the different scenarios proposed. In addition, stratification based on starting ferritin levels shows the importance of the patient's treatment history for the prediction of long-term complications.

When looking at arthralgia/myalgia (Figure 6 – left panels) the different scenarios are characterised by similar profiles, i.e., with increasing incidence of adverse events at increasing doses; but the magnitude of the effect is slightly altered at different levels of compliance. By contrast, no major differences are observed for the dose-independent AE (anaphylaxis: Figure 6 – right panels).

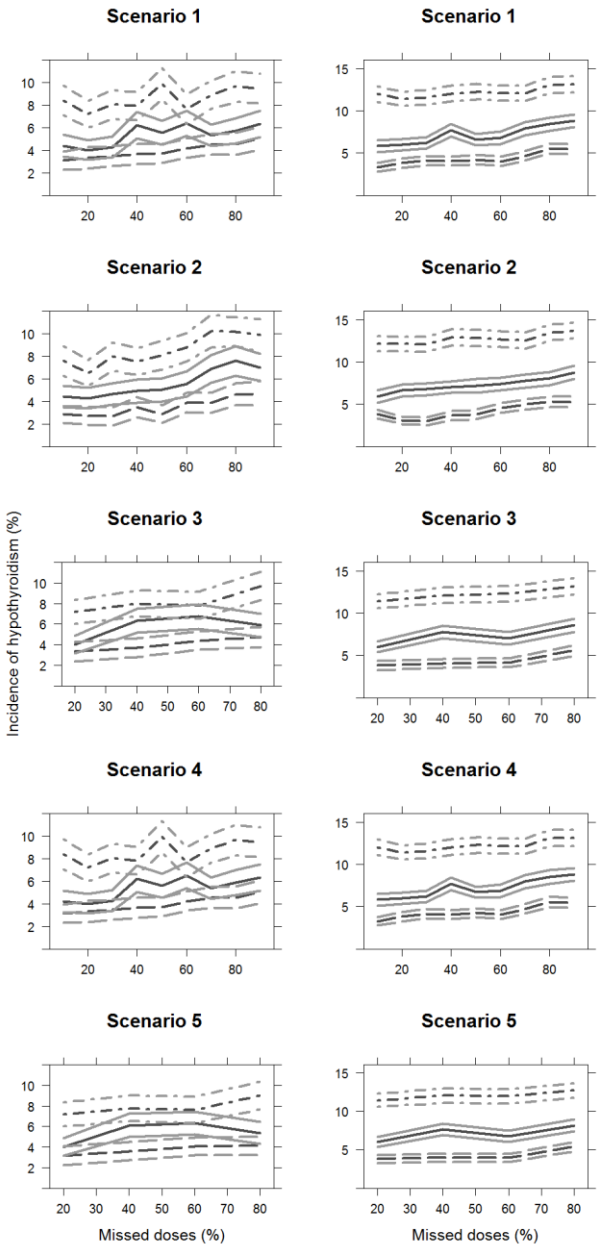

Figure 4. Effect of different patterns of compliance on hypothyroidism in the population under investigation for an observational period of maximum 10 years. Left and right panels show results based on stratification of patients into two age categories, i.e., below and above 12 years of age, respectively. In all scenarios: the dashed, solid and dotted-dashed lines represent respectively the three subgroups of patients with adequate, unknown and poor chelation history; the dark grey lines represent the mean and the light grey lines represent the 95% confidence interval of the mean. The 5 scenarios presented here are detailed in the methods and in Table 2.

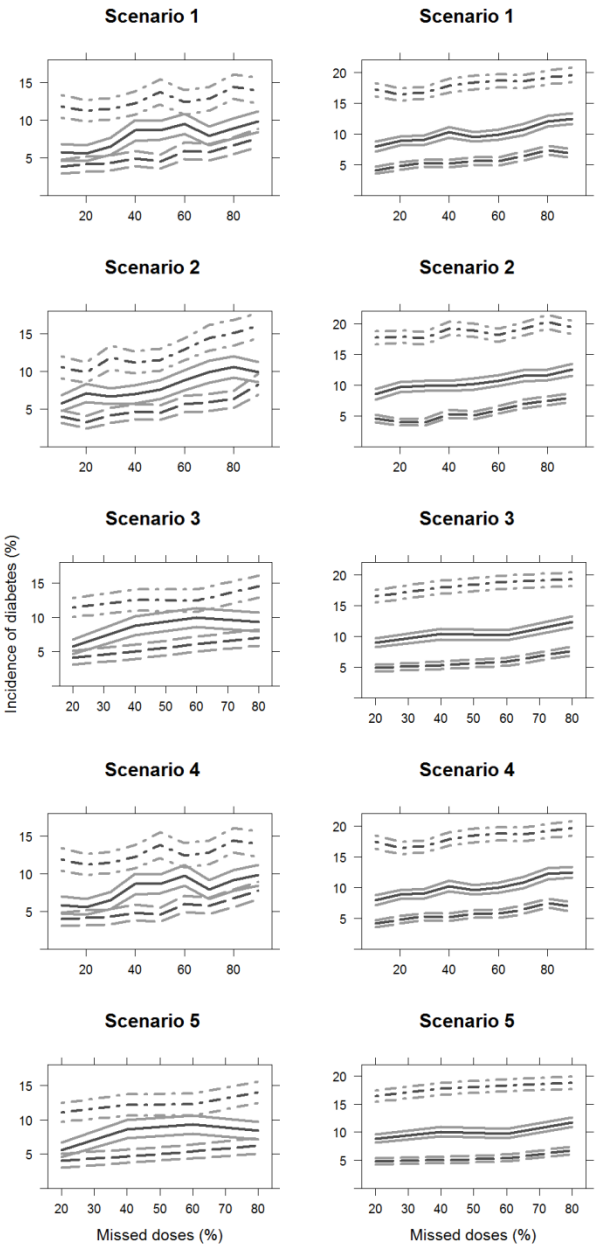

Figure 5. Effect of different patterns of compliance on diabetes in the population under investigation for an observational period of maximum 10 years. Left and right panels show results based on patient stratification into two age categories, i.e., below and above 12 years of age, respectively. In all scenarios: the dashed, solid and dotted-dashed lines represent the three subgroups of patients with adequate, unknown and poor chelation history; the dark grey lines represent the mean and the light grey lines represent the 95% confidence interval of the mean. The 5 scenarios presented here are detailed in the methods and in Table 2.

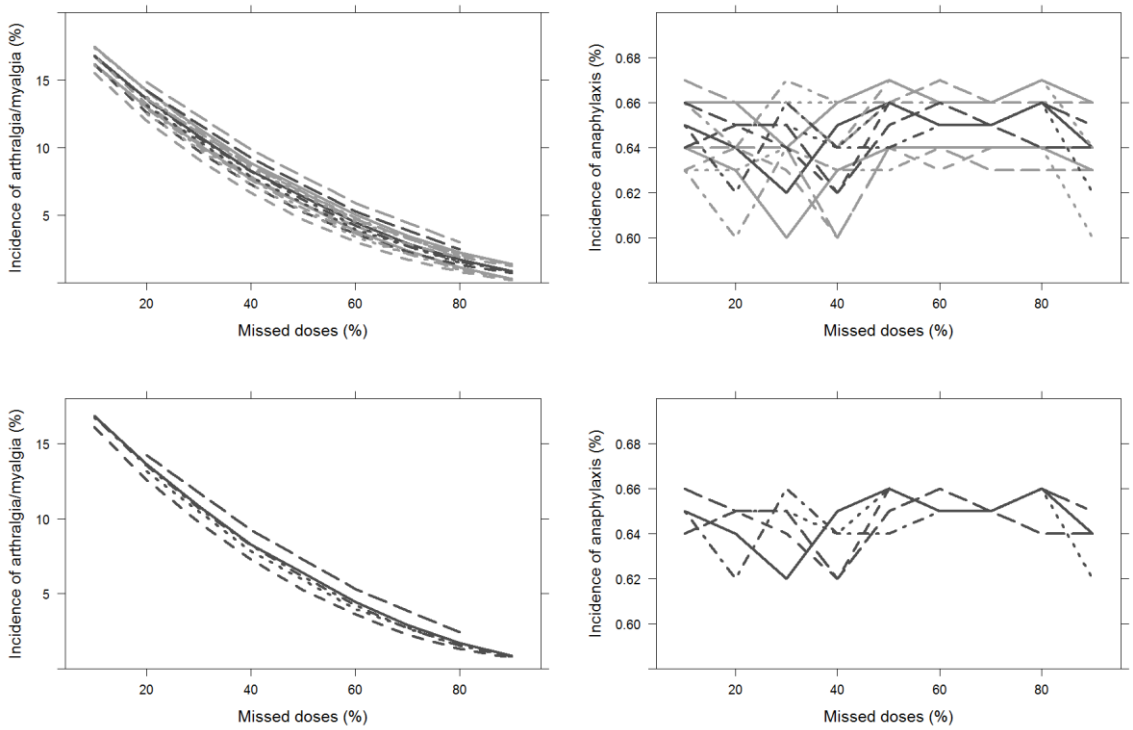

Figure 6. Effect of different compliance patterns on arthralgia/myalgia (left panels) and anaphylaxis (right panels) in the population under investigation for an observational period of maximum 10 years. The solid, dashed (small), dotted, dotted-dashed, and dashed (large) lines represent the scenarios investigated from 1 to 5 respectively. In all panels the dark grey lines represent the mean and the light grey lines represent the 95% confidence interval of the mean. Mean and 95%-CI of the mean are presented in the top panels, whereas the bottom panels show only the mean value.

8.4 Discussion and Conclusion

A model-based approach was implemented to evaluate simultaneously the short- and long-term unfavourable effects of iron chelation therapy. Epidemiological and pharmacological data have been combined to appropriately estimate the parameters of interest in the survival models. In contrast to traditional data meta-analysis, summary statistics is used to integrate data from different sources; here we rely on literature summaries to fit a population model for events whose incidence is relatively low to be derived from individual clinical trials. In fact, the epidemiological data was deemed essential for an unbiased quantification of the incidence of hypothyroidism and diabetes in the thalassaemic population. Both models were successfully validated, as shown in Figures 1 and 2.

Whereas external model validation procedures could not be easily implemented for this type of analysis, basic diagnostics plots suggested that the model was sufficiently robust support its use for simulation purposes. In fact, the use of literature summaries, i.e., point estimates,

as reference input data for fitting has been applied previously in a number of therapeutic areas in investigations with similar scope (48–50).

Treatment as a disease modifying factor

Our simulations show that long-term complications associated with inadequate chelation due to suboptimal dosing or poor compliance has major implications for patients in the lower age group, whereas almost no effect is observed for those patients in the higher age group. These results suggest that this phenomenon is partially masked by the baseline age of the population, which in turn reflects the chelation history of the patients. This is also evident by the difference in the overall incidence of the comorbidities among the three subgroups evaluated in each scenario, depending on their chelation history. These findings are in agreement with previous report on the consequences and cost of noncompliance to iron chelation (51,52). In clinical practice, improvement of compliance with chelation therapy is considered the best prevention for hypothyroidism. Guidelines also recommend regular follow-up and optimising chelation therapy in patients showing sub-clinical hypothyroidism, i.e., basal levels of TSH 5 to 7 mUI/ml.

In theory, our analysis suggests that changes in the treatment of patient at a late phase of the disease could potentially have little or no impact on the probability of developing hypothyroidism or diabetes. Hence, effective treatment at the start of chelation therapy may determine long-term onset of co-morbidities. Whilst the proposed simulations scenarios have been limited to a predefined set of compliance patterns with overall dose intake ranging from 10% (worst case scenario) to 90 % in patients with perfect adherence to treatment, literature data on deferoxamine reveals that mean compliance in patients ranges from 59 to 78 % (51).

The proposed scenarios also provide an opportunity to assess prospectively the correlation between short- and long-term complications. For instance, until now it is unclear whether changes in the dosing regimen can be implemented to provide benefit for a given patient in the short-term without significantly affecting the long-term disease progression. Such a correlation can be seen in the scenarios shown in Figures 3 to 5 for the long-term complications. Focus of treatment is mostly on correcting for changes in ferritin levels, but dose rationale currently does not assess how different dose levels may lead to higher or lower incidence of long term co-morbidities.

Limitations

The simulation scenarios presented here represent a simplification of a complex therapeutic reality in which the nature and number of co-morbidities and drug-specific AEs are much higher than those included in our analysis (53–55). Nevertheless, we believe that the

selection of a subset of AEs has enabled us to demonstrate how inferences by modelling and simulation can be used to characterise the overall safety profile of a compound. Furthermore, our approach shows how to explore safety concerns pro-actively in a quantitative manner even in the absence of sufficient data from randomised clinical trials. We acknowledge, however, that the lack of available clinical data imposed the integration of epidemiological and literature data to develop the final models based on population summary data, which may mask some specific features of the disease or treatment at the individual patient level, especially if one takes into account potential correlations or interaction between covariates. Therefore, the impact of such an interaction, as well as of the correlation between endpoints could not be evaluated. The availability of more informative, individual patient data could have provided further support for our assumptions, but we do not anticipate that such data would alter the final conclusions from the proposed simulation scenarios.

The shortcoming from individual data may have been compensated by the incorporation of time-dependent effects (and covariate factors), which allowed a clear distinction between disease-specific (long term) and drug-specific (short term) AEs.

A possible weakness remains in that very few data were available from long term safety follow up studies including paediatric and adults. Such data might have provided better estimates of the parameters and covariate factors determining the timing and age of onset of co-morbidities.

We also acknowledge that the stratification of AEs by their grade of severity would be more relevant in clinical practice. Here we have assumed a grade 2-3 for all simulated AEs to reduce the complexity of the scenarios. The same applies for the duration of the AEs and the clinical implications that the event would have for individual patients, such as dose titration over even change of chelator. This simplification was necessary to ensure that focus were given the time-dependencies associated with the long term consequences of inadequate chelation therapy (56,57).

Perspectives

In this analysis we showed that M&S provides the necessary tools to overcome the methodological and practical hurdles in the evaluation of the safety profile of a compound. We foresee the advantages of applying such an approach in the context of a full benefit-risk (BR) appraisal, where the lack of a systematic and more structured approach is acknowledged by different parties (58–62). Of particular relevance for the implementation of BR assessment, is the possibility of exploring rare dose-independent AEs. It is worth mentioning that in controlled trials and especially in paediatric trials, where limited numbers of patients are enrolled, these events might not even be observed. We believe that in such cases, modelling & simulation enables the integration of available information (e.g.,

extrapolation of adult data) to explore in a quantitative manner the implication of (clinically relevant) what-if scenarios (10,11).

Despite the limited number of scenarios presented here, several aspects can be considered and analysed by clinical trial and not-in-trial simulations. Such a framework may allow common questions in paediatric research to be evaluated in a systematic way, especially those related to developmental growth or age, which may lead to changes in the incidence of AEs over time. Another important application is the assessment of susceptibility of subgroups or population minorities which may not be appropriately represented in the trial population (63).

Conclusions

In summary, our investigation has illustrated the advantages of a model-based approach for the characterisation of the safety profile of drug in children. The use of modelling and simulation does not only provide the basis for the systematic integration of clinical and epidemiological data as a means to overcome the limited data availability in this population, but also allows one to disentangle disease-specific from the drug-specific adverse events, which are often intertwined, but have different impact on long-term outcome of treatment. Irrespective of the level of understanding or the mechanisms underlying adverse events, the availability of a simulation framework to evaluate the safety profile of a treatment offers a unique opportunity to explore scenarios which may not be feasible or even acceptable in real life, but which nevertheless provide insight into the role of the drug, the patient and the disease in the outcome of an intervention. Such information may be essential for accurate assessment of the benefit-risk profile of a medicinal product in children.

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