Exploring the Implications of Poor Patient Acceptability on Adherence and Clinical Outcomes: A Pharmacometrics case Study with Deferasirox

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INTRODUCTION

- Medication adherence is the process by which patients take their medicines as prescribed. Nonadherence is common and poses significant public health issues.
- In children, patient acceptability is crucial for adherence.
- While no studies have defined acceptance limits based on pharmacokinetic (PK) and pharmacodynamic (PD) response of a drug, it is well recognised that poor acceptability can lead to suboptimal adherence and negative treatment outcomes.

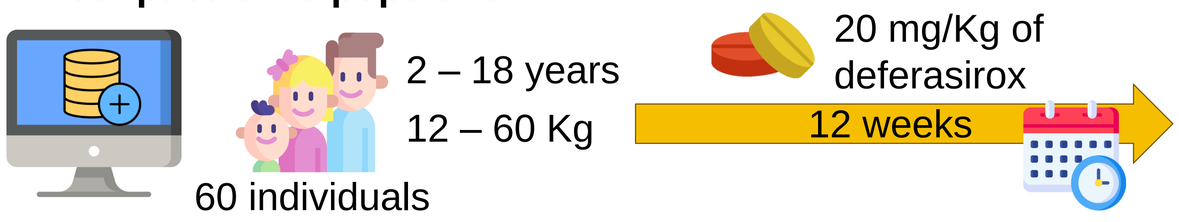
AIM: Use of modelling and simulation to quantify the potential negative impact of poor acceptability on treatment response to deferasirox in patients with hemoglobinopathies.

DEFERASIROX

- Oral iron-chelating agent for haemoglobinopathies.
- Advantage: preferred for its once-daily dosing.
- Challenge: unpleasant taste reduces adherence, especially in young patients [1].

METHODS

Virtual paediatric population



- Used a nonlinear mixed-effects modelling approach in NONMEM v.7.5.1.
- Used a previously developed population PK model [2] to derive key exposure metrics: area under the curve (AUC), steady-state concentration (Css), maximum plasma concentration (Cmax).
- Age- and weight- related changes in PK described using allometric scaling.

- Applied an Emax model to predict ferritin levels and quantify the impact of varying adherence scenarios on treatment response.
- Various nonadherence scenarios related to acceptability issues were tested (see Figure 1).

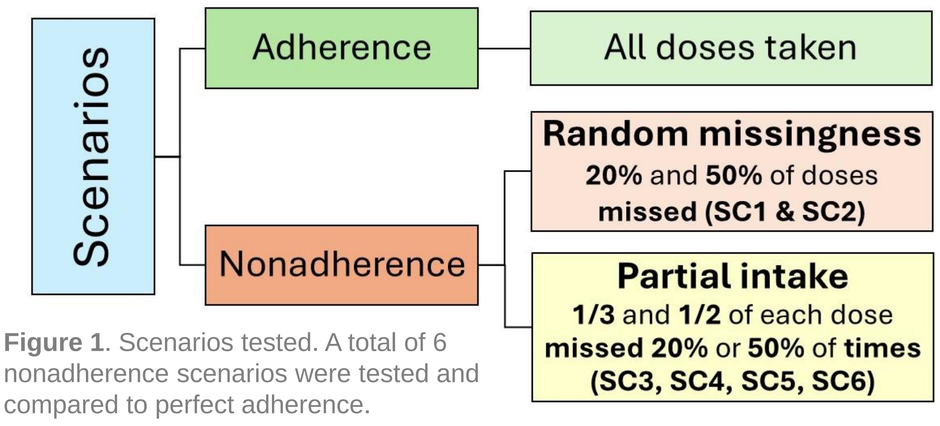


Figure 1. Scenarios tested. A total of 6 nonadherence scenarios were tested and compared to perfect adherence.

RESULTS

PK results

- All scenarios resulted in different drops of deferasirox plasma concentrations compared to perfect adherence, Figure 2.

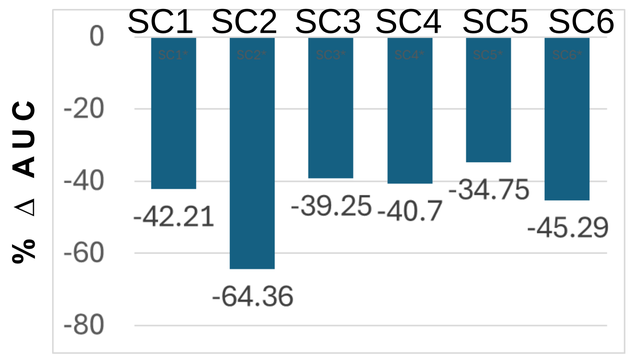


Figure 2. Percentage of change for AUC compared to perfect adherence. SC1 and SC2: 20% and 50% of doses missed. SC3 and 4: 1/3 of each dose missed 20% and 50% of times respectively. S5 and 6: 1/2 of each dose missed 20% and 50% of times respectively.

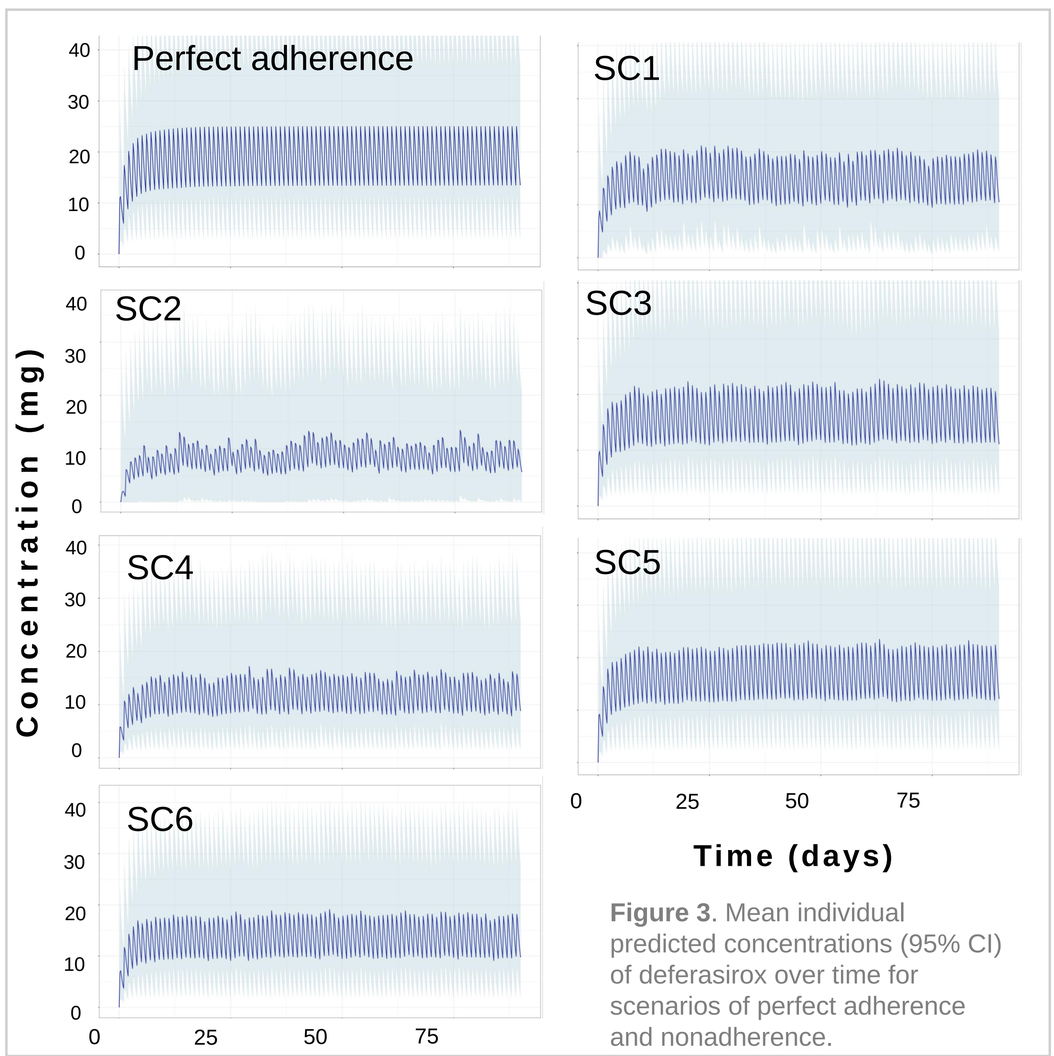


Figure 3. Mean individual predicted concentrations (95% CI) of deferasirox over time for scenarios of perfect adherence and nonadherence.

PD results

- Patients' baseline ferritin levels can vary considerably. Depending on these initial levels, the time course and magnitude of ferritin changes after deferasirox dosing may differ.

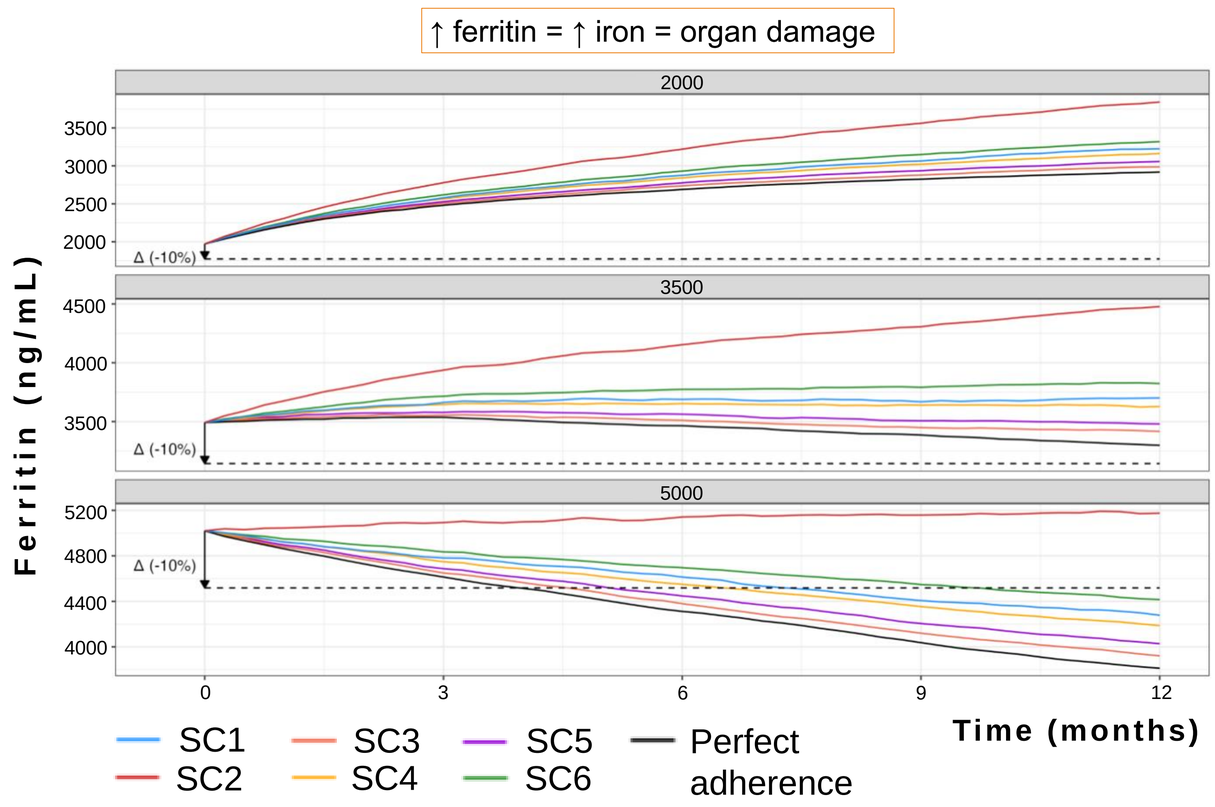


Figure 4. Predicted ferritin changes over time under conditions of perfect adherence and various non-adherence scenarios to deferasirox. The three plots represent different baseline ferritin levels, all with a consistent deferasirox dose of 20 mg/kg.

- Nonadherence scenarios result in various delays in reducing ferritin levels compared to perfect adherence.

CONCLUSIONS AND NEXT STEPS

- Different adherence levels variously influence the time needed to normalise ferritin, prolonging the risk of organ damage for extended periods of elevated iron levels.
- Next steps: Apply these scenarios to drugs with different PK/PD profiles to assess implications across various medications.

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REFERENCES
1.Tsouana, E., Kaya, B., Gadong, N., Hemmaway, C., Newell, H., Simmons, A., ... & Telfer, P. (2015). Deferasirox for iron chelation in multitransfused children with sickle cell disease; long-term experience in the East London clinical haemoglobinopathy network. European journal of haematology, 94(4), 336-342.
2.Borella E, Oosterholt S, Magni P, Della Pasqua O. Characterisation of individual ferritin response in patients receiving chelation therapy. Br J Clin Pharmacol. 2022 Aug;88(8):3683-3694. doi: 10.1111/bcp.15290. Epub 2022 Mar 26. PMID: 35199367; PMCID: PMC9544664.