Deferasirox pharmacokinetics in patients with adequate versus inadequate response

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Introduction

Iron chelation is essential for patients with transfusion-dependent anemias, who inevitably develop iron overload and the risk of life-threatening end-organ damage. Effective deferoxamine chelation has been available for more than 30 years but subcutaneous or intravenous administration is required, due to the minimal absorption in the gastrointestinal tract. This causes poor adherence and reduced efficacy.1 Deferasirox, the only oral chelator approved in the United States, has been commercially available since 2006. Phase 2 and 3 studies determined that doses of 20 to 30 mg/kg per day generally produced a net negative iron balance.2-5 The maximum dose approved as a label indication is 30 mg/kg per day, though doses up to 40 mg/kg per day were studied in the initial iron balance trial in thalassemia.6 Clinicians are aware (though supporting study data are few) that many patients do not achieve satisfactory iron balance at 30 mg/kg per day.7,8 In our center, 30% of chronically transfused patients are treated with deferasirox at doses higher than 30 mg/kg per day, initiated because of rising hepatic iron content despite therapy with maximum labeled dose.

We investigated the mechanisms of variable deferasirox response by obtaining prospective pharmacokinetic (PK) data in patients with adequate versus inadequate response to deferasirox at maximum approved dosing.

Methods

Study design

This was a prospective cohort, interventional study. Patients were admitted to the Children’s Hospital Boston Clinical and Translational Science Unit after a 48-hour drug washout period, and underwent a deferoxamine challenge, 24-hour pharmacokinetics (PK) study after a fixed weight–based oral dose of deferasirox, a nuclear medicine hepatobiliary scan, and pharmacogenomic analysis.

To verify patient adherence to home deferasirox regimen, patients were instructed after discharge to resume their regular home dose of oral deferasirox and to arrive at the next 3 clinical transfusion visits with their home daily dose of deferasirox. At each visit, serum trough drug levels were measured without special reminders for patients to take the drug on the day before their visits.

Participants

Between March 2008 and June 2008, we recruited patients from Children’s Hospital Boston, who had transfusional iron overload, and had been on deferasirox for at least 6 months at some point in their chelation history. Fifteen patients were recruited in total: 10 patients were recruited as inadequate responders and 5 were recruited as control patients with adequate response to deferasirox therapy. Inadequate response was a priori defined as (1) having a rising ferritin trend or rising liver iron on deferasirox > 30 mg/kg per day2-5 or rising liver iron on deferasirox doses > 30 mg/kg per day with control transfusion-dependent patients (n = 5) with adequate response. Subjects were admitted for 4 assessments: deferoxamine infusion and urinary iron measurement to assess readily chelatable iron; quantitative hepatabiliary scintigraphy to assess hepatic uptake and excretion of chelate; a 24-hour deferasirox PK study following a single 35-mg/kg dose of oral deferasirox; and pharmacogenomic analysis. Patients with inadequate response to deferasirox had significantly lower systemic drug exposure compared with control patients (P < .0001).

Cmax, volume of distribution/bioavailability (Vd/F), and elimination half-life (t1/2) were not different between the groups, suggesting bioavailability as the likely discriminant. Effective dosing regimens for inadequately responding patients to deferasirox must be determined. This trial has been registered at http://www.clinicaltrials.gov under identifier NCT00749515. (Blood. 2009;114:4009-4013)
(1500 μg/L); or (2) rising liver iron documented by biopsy or change in T2* or Ferriscan magnetic resonance imaging (MRI); and (3) on a dose of more than 30 mg/kg per day of deferasirox.

Five control patients were recruited from among adequate responders defined as (1) having a ferritin trend below 1000 ng/mL (1000 μg/L); or (2) documented declining liver iron burden by MRI or biopsy; and (3) on a dose of 30 mg/kg per day or less of deferasirox.

Written informed consent was obtained from each subject or their guardian in accordance with the Declaration of Helsinki and the guidelines set forth by the Committee on Clinical Investigations at Children’s Hospital Boston, which approved the study.

Deferoxamine challenge

Upon admission, patients were evaluated for mobilizable iron by a 12-hour intravenous infusion of deferoxamine 50 mg/kg with concomitant urine collection, which was tested for iron content by atomic absorption spectrometry.9,10

Deferasirox PK

Patients were administered a single oral dose of deferasirox (target dose 35 mg/kg as standard dispersible tablets) mixed according to insert instructions, in the fasting state. Twenty-four–hour PK measures included plasma levels of deferasirox and its iron complex, Fe-[ICL670]2, measured by high-performance liquid chromatography method (Novartis Pharma AG).11

All patients were sampled for serum levels of deferasirox and its Fe-[ICL670]2 complex at 0, 1, 2, 4, 6, 8, 12, and 24 hours after infusion. The PK analysis consisted in the assumption of a one-compartment open model with first-order absorption and elimination and no lag time.12 A prior noncompartmental analysis was conducted on the same data set to obtain initial estimates of the parameters. All patients were initially naive-pooled to estimate the average population PK parameters and their descriptive statistics, and then were divided according to their preassigned response group. The 2 groups were compared using the Student t test assuming unequal variances and alpha = 5%.

We calculated area under the curve (AUC), elimination half-life (t1/2), clearance, and volume of distribution (Vd) in each participant. Clearance and volume of distribution were normalized by the bioavailability (represented as “F” in Table 2A) given the oral administration. WinNonlin 5.1 (Pharsight Co) was used for noncompartmental analysis of the data, whereas nonlinear mixed effects modeling was carried out using NONMEM VI (Globomax-Icon) software package.

Liver clearance

Patients underwent quantitative assessment of liver function scan as an assessment of handling of their capacity to clear a chelate-chelator complex unrelated to deferasirox. Hepatic clearance function was assessed with quantitative hepatobiliary scintigraphy using 99mTc-disofenin (99mTc-Hepatolite; Bristol-Myers Squibb Medical Imaging) at a dose of 1.85 MBq/
Pharmacogenomic analysis

PK analysis results of free deferasirox are shown in Table 2. The mean 24-hour deferasirox concentration time curves of each group are illustrated in Figure 1A and the individual curves are shown in Figure 1B.

The systemic drug exposure among patients between the 2 groups, reflected by AUC, was significantly different, with no overlap between responders and inadequate responders, as shown in Figure 1C. The other PK parameters studied (eg, volume of distribution, clearance, and elimination half-life; Table 2) were not significantly different between the groups. To test the robustness of our findings, we replicated the analysis using both free deferasirox and drug-iron complex, and obtained similar results (typically, the Fe-[ICL670]₂ complex concentration was below 3% of free deferasirox in the serum at all sampling times). Two patients had AUCs that differed notably from their cohort. A 3-year-old female inadequate responder exhibited rapid absorption and high maximum concentration (Cmax) with rapid clearance, resulting in low net exposure. One 13-year-old male inadequate responder by enrollment criteria had PK studies most similar to the adequate responder group. In a previous deferasirox study, this patient was noted to have high and variable return pill counts, suggesting poor adherence. Further, this patient was the only one to have home regimen trough levels of zero on the follow-up adherence check, consistent with nonadherence. All other patients had levels consistent with a steady-state level from administration of a home treatment regimen. Importantly, oral deferasirox was well tolerated at maximally Food and Drug Administration (FDA)–approved doses by all patients, including children, with no overt side effects.

Deferoxamine challenge

The urine iron excretion content from the deferoxamine infusion challenge ranged from 0.09 to 0.38 mg/kg in the controls to 0.12 to 0.89 mg/kg in the inadequate responders. This difference in iron excretion was not statistically significant.

Hepatobiliary scan results

Hepatobiliary scans showed a mean fractional blood pool clearance of 0.208 plus or minus 0.021 (reference range, < 0.250) and mean fractional hepatic uptake of 0.926 plus or minus 0.012 (reference range, > 0.900). Tracer was then cleared from the liver with a mean half-time of 27.7 minutes plus or minus 1.5 minutes (reference range, < 35 minutes) and mean one-hour residual of 0.155 plus or minus 0.23 (reference range, < 0.250). None of these parameters of hepatic function correlated with the response to deferasirox (supplemental Table 2). In principle, if a correlation were observed, it might reflect a genetic or physiologic difference in hepatobiliary transport.

Results

Fifteen patients were enrolled in the study, 10 inadequate responders and 5 controls. Baseline patient characteristics are summarized in Table 1 (for more detailed information on individual characteristics, see supplemental Table 1, available on the Blood website; see the Supplemental Materials link at the top of the online article).

### Table 1. Baseline characteristics of patients enrolled

<table>
<thead>
<tr>
<th></th>
<th>Adequate responders, n = 5</th>
<th>Inadequate responders, n = 10</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>9-36 y</td>
<td>3-36 y</td>
</tr>
<tr>
<td>Younger than 20</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>21-40</td>
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<td>3</td>
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<td>7</td>
</tr>
<tr>
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<td>3</td>
</tr>
<tr>
<td>Ethnicity</td>
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<tr>
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<td>4</td>
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<tr>
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<td>1</td>
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<td>White</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Baseline disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>4</td>
<td>19†</td>
</tr>
<tr>
<td>Estimated hepatic iron concentration*</td>
<td>1.8-4.6</td>
<td>2.9-19.5</td>
</tr>
<tr>
<td>Less than 4 mg/g dry wt liver</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4-7 mg/g</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>More than 7 mg/g</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

*Assessed by T2* MRI or liver biopsy.†Includes one patient with alpha-thalassemia major: this patient was not on deferasirox at the time of enrollment in the study but had been on the drug for many months until developing acute liver toxicity.

### Table 2. Deferasirox pharmacokinetic parameters

<table>
<thead>
<tr>
<th></th>
<th>Vd/(L)</th>
<th>Vd/(L/kg)</th>
<th>CL/(L/h)</th>
<th>T1/2[elim]/h</th>
<th>AUC(μM·h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders, n = 5</td>
<td>6.57 ± 2.67</td>
<td>0.13 ± 0.05</td>
<td>0.61 ± 0.22</td>
<td>7.83 ± 2.95</td>
<td>1123.11 ± 63.4</td>
</tr>
<tr>
<td>Inadequate responders, n = 10</td>
<td>10.33 ± 7.42</td>
<td>0.32 ± 0.25</td>
<td>1.30 ± 1.18</td>
<td>6.08 ± 2.01</td>
<td>479.59 ± 259.42</td>
</tr>
<tr>
<td>P</td>
<td>.178</td>
<td>.062</td>
<td>.104</td>
<td>.275</td>
<td>.001</td>
</tr>
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</table>

Mean ± SD of responders versus inadequate responders with corresponding P based on the unpaired t test.

Vd indicates volume of distribution; F, bioavailability; CL, clearance; t, elimination half-life; and AUC, exposure, measured as area under the curve.
Pharmacogenomic analysis

Pharmacogenomic analysis of the UGT1A1 promoter region and breast cancer resistant protein (BCRP) and multidrug resistant protein 2 (MRP2) genes, based on published, clinically relevant single nucleotide polymorphisms, was not significant (see supplemental Table 3 for a complete list of single nucleotide polymorphisms and other polymorphisms analyzed).

Discussion

That important differences in deferasirox PK might be observed among patients was suggested by the first phase 1 trial of deferasirox, a trial that included patients on 40 mg/kg who had highly variable plasma drug levels and fecal iron excretion.6 This is the first study that clearly defines a PK differential in patients with iron overload treated with deferasirox and identifies stratified pharmacokinetic parameters in adequate versus inadequate responders. The key finding of this study is that responders to approved deferasirox dosing regimens are distinguished from inadequate responders by their systematic drug exposure, as reflected by significantly different AUC between the groups. Although drug levels are a common tool used to assess exposure, this is the first study in chelation therapy using drug levels for this purpose.

The minor variability in the volume of distribution of intravenous deferasirox among subjects in other published reports2,16 and similar elimination kinetics in our data (Table 2) rule out these parameters from being potential explanatory mechanisms for the differences between the 2 groups, leaving bioavailability as the likely parameter responsible for these differences. Differences in bioavailability may be related to several potential factors affecting absorption and first-pass effect, such as intestinal transit time, lipid solubility, or differences in anion organic transporter activity due to pharmacogenomic polymorphisms.

Our adjunct deferasirox studies provide important additional information. A priori it was possible that differences in mobilizable iron pools, or hepatic handling of metal-chelator complexes globally, or poor baseline adherence to prescribed deferasirox might all account for apparent differences between inadequate and adequate responders. Our deferoxamine trial for urinary iron mobilization, hepatobiliary scan results, and follow-up trough levels on at-home dosing failed to detect such differences between the groups. The sample size is not powered to definitively rule out a role for these mechanisms in deferasirox responsiveness, however, these results suggest that their contribution, if any, is likely small. Furthermore, pharmacogenetic evaluation failed to find allele distribution differences in genes related to deferasirox metabolism. However, our sample would be underpowered to detect a low but significant influence of relevant allele distribution rates between the 2 studied populations. The part II compliance check is not the exhaustive evaluation of actual adherence that MEMS (Medication Event Monitoring System) caps or other approaches might be.

We call attention to several limitations in this study. First, as an intravenous preparation of deferasirox is not commercially available, we were unable to include an intravenous deferasirox arm to determine individual and group differences in bioavailability by comparing systemic exposure after oral and intravenous administration of deferasirox (AUCp/o/AUCiv). A recent first-in-human PK study12 that included experimental intravenous deferasirox formulation in 17 patients reported absolute bioavailability of oral deferasirox around 70%, with 90% confidence interval of 62% to 80%, a range potentially broad enough to account for variable response to a given oral dose, as seen in our patients. Second, the relatively small sample size did not allow us to test the effect of other potential covariates, such as age, on the pharmacokinetics of deferasirox. Third, our subjects had a variety of underlying hemoglobinopathies. We recognize that, for example, sickle cell disease and thalassemia syndromes exhibit disparate iron distribution and kinetics. However, the present study evaluates deferasirox kinetics, not iron per se, and a much larger study will be required to evaluate this phenomenon in different disorders. Finally, the sole patient classified by enrollment criteria as an “inadequate responder,” who had exposure levels commensurate with the adequate responder group (and a trough level of zero indicating nonadherence), contributes to an underestimation of the true difference between the groups found in our study (as this patient was essentially “misclassified” based on exposure criterion). We, therefore, speculate that the magnitude of the significant difference in systemic exposure between the 2 groups is even greater than reported.

Identifying patients as responders versus inadequate responders (either by their clinical response to therapy or via early determination of individual bioavailability through oral deferasirox AUC studies) can help clinicians predict their patients’ response to therapy, and optimize it by tailoring personalized treatment regimens. Some examples of alternative dosing regimens include twice daily dosing to avoid postigestion diarrhea, a common adverse effect with high deferasirox doses, combination chelation with other agents such as deferoxamine, or higher dosing in patients with low systemic exposure and inadequate response.17 Since submission of this paper, the maximum FDA-approved dose of deferasirox has been increased to 40 mg/kg per day. It is unclear what data were provided to support this change but it will give providers more flexibility to change the dose in patients who may exhibit the poor pharmacokinetic profile seen in this study. The economic implications of this finding are worth mention: at a US wholesale price of 8.9 cents per milligram, for a 50-kg person, the difference between 30 mg/kg per day compared with 40 mg/kg per day is approximately $16 242 per year. This is a substantial increase in the already wide gap between deferasirox and deferoxamine costs per patient. However, further studies taking into account the savings from complications and hospitalizations need to be done to make an accurate health burden cost assessment.8 Further studies are also warranted to assess safety and efficacy of these potential approaches.

Acknowledgments

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Authorship

Contribution: D.C. and E.J.N. designed the study, analyzed the data, wrote the paper, and commented on the final draft; A.L.S. and J.B. participated in study coordination and data collection; M.S., Y.F., A.K.B., L.P., and F.D.G. conducted data analysis and contributed to experimental design and paper review and editing; and C.P. contributed to study design and paper review.

Conflict-of-interest disclosure: C.P. is a full-time employee of Novartis Pharmaceutical Corporation. The remaining authors declare no competing financial interests. The study was an investigator-initiated trial partially funded by Novartis, which provided the study drug and paid for and conducted the high-performance liquid chromatography analysis of deferasirox and deferasirox-iron levels. The remainder of the study, including salary support for D.C. and E.J.N., was provided by National Institutes of Health (NIH) funding, K12 and K24 (see “Acknowledgements” for fund numbers).

M.S. died March 10, 2009.

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