Pilot Safety Trial of Deferiprone in 10 Subjects With Superficial Siderosis

Michael Levy, MD, PhD; Rafael Llinas, MD

Background and Purpose—Superficial siderosis is a neurodegenerative disease caused by toxic accumulation of hemosiderin on the surface of the brain and spinal cord for which there is no known effective treatment.

Methods—Oral deferiprone, a lipid-soluble iron chelator with ability to cross the blood–brain barrier, at a dose of 30 mg/kg per day was tested for safety in an open pilot study in 10 subjects with superficial siderosis.

Results—Over a 90-day period, deferiprone had no significant adverse effects on hematologic, liver, or neurological function. Ad hoc MRI assessments of the brain indicated a reduction in hemosiderin deposition in some subjects.

Conclusions—Deferiprone proved safe in this small population of superficial siderosis subjects. There was MRI evidence of reduced hemosiderin deposition with deferiprone. Prospectively designed efficacy studies are necessary to determine the clinical efficacy of deferiprone in superficial siderosis. (Stroke. 2012;43:120-124.)

Key Words: deferiprone ■ hemosiderosis ■ superficial siderosis

Superficial siderosis is a rare, acquired, neurotoxic progressive condition caused by subarachnoid hemorrhage, leading to hemosiderin deposition on the pial surfaces of the central nervous system. The mechanism of disease involves overwhelming toxic iron sequestering by glial cells, and the amount and location of hemosiderin deposition on MR imaging correlate with symptoms and disease burden. Clinically, the majority of patients present with a combination of hearing loss and cerebellar ataxia or myelopathy attributable to involvement of the vestibular nerve (eighth cranial nerve), cerebellum, and spinal cord.

There is no known treatment for superficial siderosis. Other than rare case reports of improvement after ablation of the source of subarachnoid bleeding, superficial siderosis appears to progress because the hemosiderin deposition present at the time of clinical presentation overwhelms the ability of the brain to clear it. Previous attempts to chelate the hemosiderin iron deposits have been limited to chelating drugs that cannot effectively cross the blood–brain barrier and they have shown no effect.

Recently, we demonstrated the safety and therapeutic efficacy of using deferiprone (L1), a lipid-soluble iron chelator that can cross the blood–brain barrier. This was the first proof-of-concept case showing that removing the iron could stabilize or reverse the disease process. Based on the single superficial siderosis patient’s response to deferiprone, we obtained approval from the Food and Drug Administration to investigate the safety of deferiprone in a cohort of 10 subjects with superficial siderosis. Although efficacy was not a primary end point of the investigation, brain MRI was also performed in some subjects to evaluate the brain iron accumulation and clinical data were collected to assess potential benefits of deferiprone on the clinical manifestations of superficial siderosis.

Materials and Methods

Ten individual investigations of the new drug were approved by the Food and Drug Administration and the Johns Hopkins Internal Review Board for this open-label pilot study conducted at the Johns Hopkins Hospital (Baltimore, MD). The total number of patients with superficial siderosis in the United States is ~50, so the 10 patients in this study represent a substantial proportion of all patients with this disease. As a pilot trial, the Food and Drug Administration permitted a maximum of 10 patients to participate. Patients with superficial siderosis were recruited by direct contact via e-mail, telephone, or in person. The main inclusion criterion for this trial was a definite diagnosis of superficial siderosis confirmed by MRI in any participant aged 18 to 65 years who had mental capacity to consent to participation in the trial. The exclusion criteria included a history of agranulocytosis/neutropenia, malignancy, or current iron deficiency anemia, a known allergic sensitivity to deferiprone, or if the subject was pregnant or breastfeeding.

Eleven eligible subjects were evaluated in the clinic for participation in this trial, but 1 was excluded because of concurrent diagnosis of multiple myeloma (Figure 1). If the source of subarachnoid bleeding was deemed correctable, then the subject was referred for appropriate therapy by neurosurgery or interventional radiology. As shown in Table 1, 3 of the 10 subjects had correctable procedures. After the initial evaluation, subjects were tested for coordination ability by the Scale for the Assessment and Rating of Ataxia, gross hearing, and myelopathy by the modified Ashworth Scale. On enrollment, all subjects were started on a liquid formulation of deferiprone at 30 mg/kg per day divided into 2 daily doses. This dose is lower than the 75 mg/kg per day used in thalassemia major studies. Weekly blood counts were drawn and processed locally to
monitor the white cell count and particularly the absolute neutrophil count. Monthly liver function tests were monitored for toxicity and monthly ferritin level were followed-up to monitor for body iron stores. Subjects were e-mailed weekly to report on adverse effects of the study drug. At the conclusion of this 90-day study, all subjects underwent a brain MRI that was reviewed in a blinded fashion (Table 2). The reviewer made the best effort to contrast the scans as evenly as possible and present cuts as similar as possible. Primary statistical analysis of safety measures was intention-to-treat and was performed using Graphpad Prism 4.0.

Role of the Funding Source

The study was sponsored in part by the manufacturer of deferiprone (ApoPharma). ApoPharma was not involved in the study design, data collection or analysis, interpretation of the data, content of the manuscript, or in the decision to publish this report.

Results

Ten subjects were enrolled from the Johns Hopkins Neurology Clinic to this pilot safety study of deferiprone in superficial siderosis (Figure 1). Characteristics of this population including age, gender, etiology, duration of disease before treatment, and symptoms are listed in Table 1. The average age of the 10 subjects was 55 years, with a range of 41 to 68 years of age. There were 5 women and 5 men. Etiologies were varied and 3 subjects had previous surgical repair of their subarachnoid blood leak. The average duration of disease before treatment was 12 years, with a range of 3 to 20 years. Symptoms universally included hearing loss (100%) and most included myelopathy (80%) and ataxia (60%). Other neurological symptoms were varied among subjects (data not shown).

An assessment of safety of deferiprone in superficial siderosis subjects was the primary outcome objective. Because deferiprone has been associated with agranulocytosis in patients with thalassemia major,9 weekly blood counts were monitored for evidence of episodes of neutropenia in this study cohort. As shown in Figure 2, there was no indication of bone marrow involvement in this study cohort for the duration of the 90-day trial. Specifically, there was no change in white blood cell counts, absolute neutrophil counts, percentage of neutrophils, or hemoglobin levels (Figure 2). Monthly liver function tests revealed 3 subjects had transient elevations in liver function test results over the course of the trial (Figure 3). Two of these subjects discontinued deferiprone therapy for 1 week, after which the liver enzymes declined. Both subjects restarted deferiprone after 1 week and had no further liver enzyme elevations. Monthly ferritin levels show a modest decline in all subjects over the course of the 90-day trial (Figure 3), but none was below the low reference range of 5 ng/mL.

Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Gender</th>
<th>Etiology</th>
<th>Duration (Time Since First Symptom)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>F</td>
<td>Pseudomeningocele*</td>
<td>8 y</td>
<td>Hearing loss (2002), ataxia, myelopathy</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>F</td>
<td>Thoracic dural tear*</td>
<td>15 y</td>
<td>Hearing loss (2005), myelopathy (2000)</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>M</td>
<td>Postneurosurgical</td>
<td>20 y</td>
<td>Hearing loss (1990), myelopathy (2009)</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>F</td>
<td>Recurrent inner ear hemorrhaging</td>
<td>3 y</td>
<td>Hearing loss, myelopathy, diplopia (2007), ataxia (2009)</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>M</td>
<td>Longitudinally extensive meningocele</td>
<td>8 y</td>
<td>Hearing loss and ataxia (2002)</td>
</tr>
<tr>
<td>Median</td>
<td>55</td>
<td>50/50</td>
<td></td>
<td>10 y</td>
<td>Hearing loss (100%), myelopathy (80%), ataxia (60%)</td>
</tr>
</tbody>
</table>

Ten individual investigations of new drugs were obtained from the Food and Drug Administration. Subjects were recruited from the neurology clinic at Johns Hopkins. The median age of the 10 subjects was 55 years, with a range of 41 to 68 years. There were 5 females and 5 males. Etiologies were varied and 3 subjects had surgical repair of their subarachnoid blood leak. The average duration of disease before treatment was 12 years, with a range of 3 to 20 years. Symptoms universally included hearing loss (100%) and most included myelopathy (80%) and ataxia (60%). Other neurologic symptoms were varied among subjects (data not shown).

F indicates female; M, male.
*Underwent surgical procedure to repair the source of bleeding.
MRI was performed when possible after the conclusion of the trial for evaluation of hemosiderin deposition. An ad hoc comparison with the most recent MRI before starting the drug was conducted to evaluate the efficacy of deferiprone in reducing the brain hemosiderin deposition of the subjects. All subjects obtained post-trial MRI, which were compared to the most recent pretrial MRI. Although the time between the last pretrial MRI and the post-trial MRI varied in this ad-hoc analysis, we still found that a 90-day course of deferiprone therapy was associated with a decrease in hemosiderin deposition by MRI in 4 of the 9 subjects. Figure 4 shows 4 representative MRI demonstrating the qualitative reduction in hemosiderin deposition at brain surfaces, indicated by the arrows. From the available data on untreated superficial siderosis, there should be no expected improvements in hemosiderin deposition by MRI over time, suggesting that the changes we see in these test subjects is attributable to the study drug. This ad hoc MRI finding is consistent with a recent case report of a superficial siderosis patient using deferiprone for 1.5 years and showed a clinical improvement using the drug, along with a reduction in hemosiderin deposition by MRI. Two subjects showed a slight increase in hemosiderin deposition by MRI, consistent with progressive superficial siderosis disease, and 3 showed no change (data not shown).

Clinical examinations were performed before starting the study drug. Baseline measures of myelopathy, hearing, and ataxia were assessed for safety purposes should the drug lead to neurological decline. Clinical examinations were not designed for determination of efficacy; thus, post-trial clinical examinations were not a necessary component of the trial. Only 2 subjects returned to Johns Hopkins for post-trial clinical examinations, one of whom (subject 6 in Table 1) had progressively worsening neurological symptoms associated with an increase in hemosiderin deposition by MRI, suggesting that the rate of hemosiderin deposition in this subject was greater than the rate of chelation by this dose of deferiprone. These limited clinical examination results do not accurately

<table>
<thead>
<tr>
<th>Subject</th>
<th>Interval (mo)</th>
<th>MR Manufacturer</th>
<th>MR Sequence</th>
<th>Field Strength</th>
<th>TE/TR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (Fig. 4A)</td>
<td>16</td>
<td>Before drug GE Medical Systems Signa Excite</td>
<td>Prop T2</td>
<td>1.5</td>
<td>127/7874</td>
</tr>
<tr>
<td>8 (Fig. 4B)</td>
<td>58</td>
<td>Before drug GE Medical Systems Signa Excite</td>
<td>T2 OBL</td>
<td>1.5</td>
<td>80/2200</td>
</tr>
<tr>
<td>2 (Fig. 4C)</td>
<td>22</td>
<td>Before drug Siemens Avanto</td>
<td>T2</td>
<td>1.5</td>
<td>100/2850</td>
</tr>
<tr>
<td>1 (Fig. 4D)</td>
<td>4</td>
<td>Before drug Siemens Espree</td>
<td>T2 TSE</td>
<td>1.5</td>
<td>102/5730</td>
</tr>
<tr>
<td>4</td>
<td>89</td>
<td>Before drug GE Medical Systems Genesis Signa</td>
<td>T2</td>
<td>1.5</td>
<td>88/3500</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>Before drug GE Medical Systems Signa HDxt</td>
<td>T2</td>
<td>1.5</td>
<td>128/6855</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>Before drug Philips Medical Systems Achieva</td>
<td>T2</td>
<td>1.5</td>
<td>120/3982</td>
</tr>
<tr>
<td>7</td>
<td>86</td>
<td>Before drug Siemens Magnetom</td>
<td>T2</td>
<td>0.7</td>
<td>96/4145</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>Before drug GE Medical Systems Signa HDxt</td>
<td>T2</td>
<td>3</td>
<td>111/4600</td>
</tr>
<tr>
<td>10</td>
<td>19</td>
<td>Before drug GE Medical Systems Signa HDxt</td>
<td>T2</td>
<td>1.5</td>
<td>95/5000</td>
</tr>
</tbody>
</table>

Subject N refers to Table 1.
MR indicates magnetic resonance; MRI, magnetic resonance imaging; TE, echo time; TR, repetition time.
represent the effect of the drug on neurological function experienced by all the subjects using the drug. By telephone discussion, 4 subjects claimed to have subjective improvement in neurological function ranging from better coordination and gait to better hearing, more energy, clearer thinking, and reduced spasticity. Four reported no changes in neurological function and 2, including the subject described, reported progressive worsening of previous symptoms. Further study with a prospective placebo-controlled design over a longer period of time to evaluate the efficacy of deferiprone in superficial siderosis is needed to ascertain a possible clinical benefit.

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**Disclosures**

M.L. received $1000 in a speaking honorarium from the manufacturer, ApoPharma. R.L. has no conflicts of interest to report.

**References**


Figure 4. T2*-weighted MRI images from 4 trial subjects (A–D) before and after drug trial. Arrows point to the areas of heavy hemosiderin deposition, which is demonstrated by a rim of hypointensity on the surface of the brain. Please refer to Table 2 for MRI parameters. Note the decreased deposition in each case.
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