Deferasirox: The New Oral Iron Chelator

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Deferasirox is a new tridentate oral iron chelator developed by computer remodeling recently approved by FDA for children above 2 years. Phase II/III trials have demonstrated similar efficacy to desferrioxamine and better chelation efficiency. Adverse events were minor and growth remained unaffected. Data on cardiac iron chelation is limited although some studies have shown it comparable to deferiprone. The benefit to risk profile of deferasirox is favorable. This promising new drug might decrease the burden of subcutaneous or intravenous infusion improving compliance and hence the life expectancy in thalassemic patients.

Key words: Deferasirox, Iron chelator, Thalassemia

Life expectancy of thalassemics has improved in the last few years with regular blood transfusions. This hyper-transfusion leads to iron overload, secondary hemosiderosis and multiple organ damage. Cardiac complications remain the leading cause of mortality in transfusional iron overload(1). The focus of problem has hence shifted to better chelation therapy.

Since 1963 desferrioxamine has remained the “gold standard” iron chelator and shown to reduce iron-related morbidity and mortality(2). Unfortunately, compliance with subcutaneous infusions still remains a serious limiting factor in treatment success. Deferiprone, an oral iron chelator has been in use in India for almost 10 years. Although total iron excretion with deferiprone is somewhat less than with desferrioxamine, it has a better cardio protective effect(3). However, certain side effects like arthropathy etc. limit its use despite the ease of oral administration.

Deferasirox (ICL670), is the first oral iron chelator approved in USA by FDA in November 2005(4). It was developed by computer remodeling, after evaluating more than 700 chelators from various chemical classes and belongs to a new class of tridentate chelator, the bishydroxyphenyltriazoles(5).

Mechanism of action of iron chelators

Ferric iron has six coordination sites, which need to be chelated completely to prevent the generation of free radicals. Chelators, such as desferrioxamine, which coordinate all six sites using a single molecule (hexadentate chelators), form a more stable iron-chelate complex than ligands, which require more than one molecule. Chelators such as deferiprone possess only two co-ordination sites (bidentate chelators) tend to dissociate from iron at low concentrations and can generate free radicals. Deferasirox belongs to a new class of tridentate iron chelator requiring two molecules to form a complete complex with ferric iron. Comparison of different iron chelators is shown in Table I.

Clinical studies

After phase I studies(6,7) demonstrating safety and efficacy, deferasirox was evaluated in large multi-centric clinical phase II trials(8-11) and phase III trials(12) in patients with transfusion-dependent anemias (β-thalassemia, Sickle cell disease, etc.). All three major trials(8,9,12) enrolled adult and pediatric patients and 46.7% of patients were <16 years of age. Major studies are summarized in Table II.

A multicenteric phase III study compared the iron chelation of deferasirox and desferri-oxamine(12). Patients randomized to receive desferrioxamine with liver iron content (LIC) values <7 mg Fe/g dry weight...
TABLE I– Comparison of Iron Chelators

<table>
<thead>
<tr>
<th>Class</th>
<th>Desferrioxamine</th>
<th>Deferiprone</th>
<th>Deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron binding efficiency</td>
<td>Hexadentate</td>
<td>Bidentate</td>
<td>Tridentate</td>
</tr>
<tr>
<td></td>
<td>1:1</td>
<td>3:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Parenteral, usually SC night time infusion 5-7 nights/week</td>
<td>Oral; thrice a day</td>
<td>Oral, can be used as a single daily dose</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>Short (minutes)</td>
<td>Moderate (&lt; 2 hours)</td>
<td>Long (8-16 hours)</td>
</tr>
<tr>
<td>Myocardial iron chelation</td>
<td>Low</td>
<td>High</td>
<td>Data insufficient</td>
</tr>
<tr>
<td>Important side effects</td>
<td>Local skin reactions at infusion sites, auditory and retinal toxicity, skeletal changes, growth retardation</td>
<td>Common: Abdominal discomfort; arthropathy. Rare: Severe agranulocytosis (&lt; 1%)</td>
<td>Transient gastrointestinal events; skin rash; mild increased creatinine (clinically insignificant)</td>
</tr>
<tr>
<td>Brand Name</td>
<td>Desferal</td>
<td>Kelfer</td>
<td>Asurna (India); Exjade (other countries)</td>
</tr>
<tr>
<td>Availability</td>
<td>Available</td>
<td>Available</td>
<td>Licensed by FDA; will be shortly available in India</td>
</tr>
</tbody>
</table>

TABLE II– Phase II/III Studies on Deferasirox

<table>
<thead>
<tr>
<th>Phase</th>
<th>Patient population</th>
<th>Patient No.</th>
<th>Study design</th>
<th>Primary endpoint</th>
<th>Secondary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Porter, et al.(7)</td>
<td>β-thalassemia and other rare anemias*</td>
<td>184</td>
<td>Non-comparative</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td></td>
<td>Vichinsky, et al.(8)</td>
<td>Sickle cell disease</td>
<td>195</td>
<td>Open lable, randomized</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td></td>
<td>Piga, et al.(9)</td>
<td>β-thalassemia</td>
<td>71 adults</td>
<td>Open lable, randomized</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td></td>
<td>Piga, et al.(10)</td>
<td>β-thalassemia</td>
<td>40 pediatric</td>
<td>Open lable, randomized</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>III</td>
<td>Cappellini, et al.(11)</td>
<td>β-thalassemia</td>
<td>586 (97 patients &lt;16 years)</td>
<td>Open lable, randomized</td>
<td>Maintenance or reduction of LIC</td>
</tr>
</tbody>
</table>

* Included: Thalassemia: 85; Myleodysplastic syndrome 47; Diamond Blackfan anemia 28; Others 23.

(dw) were permitted to remain on their pre-study doses, even if these doses were higher than those specified by the protocol, since these doses were deemed to be safe and effective. LIC, the primary outcome variable for the demonstration of non-inferiority to desferri-oxamine, was assessed at baseline and after 12 months of therapy by liver biopsy. In some patients, noninvasive magnetic susceptometry by super-conducting quantum interference device (SQUID) was used. Serum ferritin was measured monthly.

Success was defined as maintenance or reduction in the LIC as per the baseline LIC. Treatment was for one year initially, to be followed by an extension phase. Non-inferiority was demonstrated in the group of patients (69%) who were allocated to the higher dose groups (deferasirox doses of 20 or 30 mg/kg and desferrioxamine dose of 35 mg/kg) with baseline LIC levels >7 mg Fe/g dw. Overall success rates for deferasirox and desferrioxamine as analyzed by biopsy and SQUID were comparable (58.6% vs.
58.9%), and the lower limit of the 95% confidence interval (−10.2%) was above the non-inferiority threshold of −15% specified. Statistically significant and similar reduction in LIC (−5.3 ± 8.0 mg Fe/g dw, \( p < 0.001 \)), serum ferritin levels and change in iron balance (defined as the ratio of iron excretion to iron intake) was observed in both arms in patients with LIC values >1 = 7 mg Fe/g dry weight. All parameters indicated an increase in patients receiving deferasirox 5 or 10 mg/kg; essentially unchanged in those receiving deferasirox 20 mg/kg; and reduced for those receiving 30 mg/kg of deferasirox.

Pooled data analysis revealed that the overall chelation efficiency (per cent iron excretion vs. theoretical iron binding capacity of chelator dose) of deferasirox was twice that desferrioxamine (27% vs. 13%)\(^{13}\). There are no studies comparing deferasirox with either deferiprone alone or deferiprone with desferrioxamine combination.

**Adverse reactions**

According to the pooled thalassemia data most frequent adverse events (>10% of all patients) were abdominal pain 23.8%, pyrexia 23.3%, headache 19.7%, cough 19.0%, diarrhea 16.6%, vomiting 13.8%, rash 12.4%, nausea 11.9%, increased creatinine 11.6%. These symptoms were generally manageable with supportive measures and have rarely required the permanent discontinuation of therapy. Deafness, neurosensory deafness or hypoacusis were reported in 0.3% only. The adverse event profile was almost similar in children.

Serious adverse events related to the drugs were reported in 13(3.1%) and 1(0.3%) of those receiving deferasirox and desferrioxamine, respectively. Adverse events that led to discontinuations included abnormal liver function tests and drug-induced hepatitis, skin rash, glycosuria/proteinuria, Henoch Schonlein purpura, hyperactivity/insomnia, drug fever, and cataract. Drug related agranulocytosis, thrombocytopenia, effect on hematologic parameters or bone changes have not been reported. Growth and development remained unaffected.

**Deferasirox and heart**

Deferasirox can readily enter into cardiomyocytes and scavenges labile cell iron\(^{14}\). It was as effective as deferiprone in removing stored cardiac iron in a gerbil animal model\(^{15}\). In a clinical trial of 23 patients treated with deferasirox, myocardial T2* improved significantly from a pretreatment geometric mean of 18.0 ms to 23.1 ms (\( p = 0.013 \)). There was no significant change in left ventricular ejection fraction before or after treatment over the same period. These studies suggest that once daily mono-therapy with deferasirox will be effective at improving myocardial T2* and by inference myo-cardial iron loading in a wide range of patients with transfusional iron overload\(^{16}\).

**Prescribing information**

**Indications and Usage**

Chronic iron overload secondary to blood transfusions (transfusional hemosiderosis) in patients >2 years. Therapy should be started when a patient has evidence of chronic iron overload (serum ferritin consistently >1000 µg/L).

**Dosage**

The initial dose is 20 mg/kg orally once daily; doses calculated to the nearest whole tablet. Adjust the dose in increments of 5 or 10 mg/kg every 3 to 6 months based on serum ferritin trends. The maximum dose is 30 mg/kg/day since there is limited experience with doses above this level. Deferasirox should be completely dispersed in water, orange juice or apple juice and be taken empty stomach 30 minutes before a meal preferably at the same time every day. The tablets should not be chewed or swallowed whole. After swallowing the suspension, any residue should be resuspended in a small volume of the liquid and swallowed. An initial higher dose of 30 mg/kg might be considered for severely iron overload patients (e.g., serum ferritin> 2500 µg/L). It is supplied as 125, 250 and 500 mg tablets for oral suspension.

Monthly monitoring of serum ferritin is recommended and the dose adjusted accordingly every 3 to 6 months, in steps of 5 or 10 mg/kg. If the serum ferritin falls consistently <500 µg/L, consider temporary interruption.

**Pharmacokinetics**

Deferasirox exhibits linear kinetics. The bio-
availability is approximately 70%. Peak plasma concentrations of deferasirox are achieved between 1-4 hours and the mean elimination half-life is 8-16 hours. Once-daily doses can be used. Deferasirox is almost exclusively bound to albumin (99%). Metabolism is by glucuronidation with subsequent biliary excretion(17). The parent and metabolites are primarily excreted in the feces and minimally excreted renally (<8%). No significant drug interactions have been identified. Although studies in rats have shown a favorable interaction between desferrioxamine and deferasirox manifesting as improved chelating efficiency of deferasirox, it should not be combined with other iron chelators, as safety of such combinations has not been established(18).

Contraindications

Use is contraindicated in patients with hypersensitivity to deferasirox.

Special populations

Renal dysfunction

Studies of deferasirox did not enroll patients with serum creatinine values above the upper limit of normal. Therefore, specific studies assessing deferasirox pharmacokinetics in renal impairment were not done. Dose-dependent increase in serum creatinine was observed in 38% cases. Most of the creatinine elevations remained within the normal range. After dose reductions (13% of cases) creatinine either returned to baseline or remained stable.

Hepatic dysfunction

Thalassemia patients with iron overload often have abnormal liver function tests due either to iron overload or concomitant viral hepatitis. Patients with mild to moderate elevations in serum transaminase levels (up to 5 times the upper limit of normal) were enrolled in the clinical studies and were treated with doses of deferasirox similar to patients without hepatic impairment. Safety, efficacy, and pharmacokinetic parameters were similar in both groups. The values showed marked fluctuations and were not progressive. Monthly laboratory monitoring of renal and hepatic function should be performed.

Special Senses

Auditory disturbances (high frequency hearing loss, decreased hearing), and ocular disturbances (lens opacities, cataracts, elevations in intraocular pressure, and retinal disorders) have been reported at a frequency of <1%. Auditory and ophthalmic testing (including slit lamp examinations and dilated fundoscopy) is recommended before starting treatment and thereafter at regular intervals (every 12 months). If disturbances are noted, dose reduction or interruption should be considered.

Pregnancy

Although animal studies have not shown any evidence of impaired fertility or harm to the fetus, there are no adequate and well-controlled studies in pregnant women.

Nursing mothers

Since it is not known whether deferasirox is excreted in human milk, caution should be exercised while administering to nursing mothers.

Cost analysis

There is no data on the cost benefit analysis using either deferiprone alone or deferiprone with desferrioxamine combination. There are no costing models available in the Indian context.

Key Messages

- Deferasirox, a new oral iron chelator approved for children above 2 years, would be available soon in India.
- Phase II/III trials have demonstrated similar efficacy to desferrioxamine and better chelation efficiency with only few adverse events. The benefit to risk profile of deferasirox appears favorable but no Indian data is yet available.
Conclusions

The benefit to risk profile of deferasirox is favorable. It has similar efficacy to desferrioxamine but is not associated with any significant complications. The cost effectiveness was favorable in costing models. This promising new oral drug will decrease the burden of subcutaneous or intravenous infusion, which might improve compliance and hence the life expectation.

Contributors: APD conceptualized the idea, edited and approved the final version. He will act as guarantor. SS and AP contributed towards literature search. AP prepared the manuscript.

REFERENCES


