Deferasirox: Oral, Once Daily Iron Chelator - An Expert Opinion

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ABSTRACT

Iron overload is a serious and potentially fatal condition that results from multiple blood transfusions required over a long period of time to treat certain types of anemias such as, that caused by β-thalassemia, sickle cell disease and myelodysplastic syndrome. Deferoxamine, which has been used since four decades as an iron chelator has limited efficacy due to its demanding therapeutic regimen, leading to poor compliance. Deferasirox, once daily oral iron chelator provides an effective alternative to Deferoxamine in the treatment of transfusional hemosiderosis. In this review, the role of Deferasirox as an ideal iron chelator has been discussed. Pubmed searches on Deferasirox were carried out for the same. Several studies demonstrated the safety and efficacy of Deferasirox in reducing iron burden in iron-overloaded patients with β-thalassemia, sickle cell anemia and myelodysplastic anemia. Thus, convenient, effective and tolerable chelation therapy with oral Deferasirox is likely to be a significant development in the treatment of transfusional iron overload, due to its ability to provide constant chelation coverage and the potential to improve compliance.

Key words: Chelation; Deferasirox; Iron; Thalassemia

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[Received January 6, 2010; Accepted January 6, 2010]
Unmet Medical Need/Therapy Gap in Clinical Practice

In 1963, the introduction of Deferoxamine (DFO), a hexadentate chelator marked a breakthrough in the management of iron overload. However, Deferoxamine requires subcutaneous or intravenous infusions. Moreover, patients with severe anemia cannot achieve iron depletion by the periodic removal of blood (therapeutic phlebotomy), because they cannot tolerate exacerbation of anemia that occurs as an unavoidable consequence of therapeutic phlebotomy. Clearly, the removal of excess body iron is vital to improve morbidity and mortality in patients with transfusional hemosiderosis. Table 1 compares deferasirox with existing iron chelators i.e., deferoxamine and deferiprone.

Goals of Chelation therapy

In clinical practice, key goal of chelation therapy is prevention of iron accumulation, as this will prevent a rise in liver iron concentration and the secondary redistribution of iron to other organs, including the pituitary, endocrine glands and the heart. In order to achieve an iron balance, two key iron pools need to be accessed by chelators.

(i) Intracellular labile iron pool (LIP)

In iron overload, the hepatocytes are the major cells of iron storage, with liver iron closely approximating total body iron. Therefore, liver is the major key target for chelation therapy.

(ii) Iron from red cell catabolism

The second major source of chelatable iron is that derived from red cell catabolism in macrophages, which is increased during ineffective erythropoiesis. Because this iron pool is rapidly (re)incorporated into ferritin and only transiently available for chelation therapy, its iron-detoxifying effect depends upon the drug availability for 24 hr a day; called as protection time.

Discovery of a novel chelator: From desferriothiocin to Deferasirox

Several efforts have been made over the past four to five decades, to synthesize orally active iron chelators. Ferferrithiocin was first discovered in 1980, followed by the synthesis of the tridentate desferrithiocin, whose activity via oral administration have raised a hope. However, animal studies confirmed the compound to be toxic. The discovery of bishydroxyphenyltriazoles, a new chemical class of iron chelators, renewed the pursuit of a safe tridentate chelator.

A combination of rational design, intuition and experience paved the way for the discovery of the basic structure of this completely new chemical class of iron chelators. More than forty derivatives of the triazole series were synthesized at Novartis. After screening more than 700 chelators from various chemical classes, Deferasirox emerged as a bishydroxyphenyltriazole entity, which best combined high oral potency and tolerability in animals.

Structure Activity Relationship (SAR)

Deferasirox is a bis-hydroxyphenyl-triazole benzoic acid derivative (Fig. 1). 1,2,4-triazoles can be regarded as condensation products of imides with hydrazines. Thionylchloride mediated condensation of salicylic acid with salicylic amide results in the formation of a hydroxyphenylbenzoxazinone, a derivative form of the imide. This intermediate is ideally activated to react with hydrazines, forming bishydroxyphenyl-triazoles in just two steps from salicylic acid.

Table 1. Comparison of Deferasirox with Existing Iron Chelators

<table>
<thead>
<tr>
<th>Feature</th>
<th>Deferoxamine</th>
<th>Deferiprone</th>
<th>Deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron binding efficiency (drug : iron)</td>
<td>1 : 1</td>
<td>3 : 1</td>
<td>2 : 1</td>
</tr>
<tr>
<td>Iron selectivity</td>
<td>Highly selective</td>
<td>Zinc is also excreted</td>
<td>Highly selective</td>
</tr>
<tr>
<td>Regimen</td>
<td>SC or IV infusion</td>
<td>Oral, 3 times a day</td>
<td>Oral, once a day</td>
</tr>
<tr>
<td>Tolerability issues</td>
<td>Local reactions</td>
<td>Joint problems</td>
<td>Skin rashes</td>
</tr>
<tr>
<td>Long-term safety profile</td>
<td>Proven</td>
<td>Severe neutropenia</td>
<td>Emerging</td>
</tr>
</tbody>
</table>

Pharmacodynamics

Deferasirox is an orally active chelator that is highly selective for iron. It is a tridentate chelator that mobilizes iron stores by binding selectively to the ferric (Fe3+) form of iron. Tridentate chelators require two ligand molecules to bind one iron atom. The selectivity for iron is high, with low affinity for trace metals, such as zinc or copper.