Exjade (ICL 670) : A New Oral Iron Chelator

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Abstract

ICL670(deferasirox) is a tridentate oral iron chelator that has shown high efficacy and therapeutic safety in preclinical and currently ongoing phase III clinical evaluation. The drug has been just approved by US FDA for use in iron-loading anaemias. It is an ideal once-daily oral chelator, the effective dose of which is between 20 and 40 mg/kg. Iron is chelated & excreted almost exclusively via the feces. This is a major advance in the field of iron chelation. ©

Although iron is vital to health, excessive amounts in the body are highly toxic. Iron overload is a feature of a number of pathological conditions; it is an inevitable and serious consequence of long-term transfusion therapy for anaemia. Iron chelation, which effectively prolongs life of transfusion-dependent thalassaemias and also improves the quality of life, is cumbersome and expensive using the current “gold standard” - deferoxamine (DFO), while the only other iron chelator that is available (Deferiprone-L1-Kelfer), is less effective and has certain adverse effects keeping it’s popularity on the lower side. There is obvious need for developing an alternative oral iron chelator, which is oral, effective and safe making it suitable for long-term use, either alone or in combination with the two chelators mentioned above. Despite hopes raised by a number of promising compounds, with few exceptions, majority proved to be either ineffective or too toxic to be of use.

Pyridoxal isonicotinoyl hydrazine (PIH) and the polyanionic amines HBED and dimethyl-HBED looked promising as they were shown to be relatively non-toxic and effective. However, both these agents are not proprietary (patentable) and hence, despite being promising, the drug industry has no or limited interest. Moreover, significant interest in L1 during last one and half decade left very limited space for further development of other orally effective and efficient chelators.

A new synthetic oral iron chelator, ICL 670 (Fig. 1), a highly efficient and selective once a day oral iron chelator, has given a ray of hope. It is currently in the late stages of a comprehensive clinical development programme. ICL 670 is a member of a new class of tridentate iron-selective synthetic chelator - the bis-hydroxyphenyl-triazoles. Two molecules of the chelator are required to form a complete complex with ferric iron. In iron-loaded rats and marmosets, oral ICL 670 is twice as effective as subcutaneous DFO. The iron excretion is predominantly fecal. Iron is chelated, both from the reticulo-endothelial cells (RE cells) as well as various parenchymal organs and the chelated iron is cleared by the liver and excreted through the bile. It also has the ability to prevent myocardial cell iron uptake, remove iron directly from myocardial cells and exchange iron with DFO. In fact, ICL 670 readily yields iron to DFO.

ICL 670 has been developed by computer modeling. It is an N-substituted bis-hydroxyphenyl-triazole selected from more than 700 compounds screened as part of a rational drug development programme. In animal models, on molar basis, it has been shown to be 5 times more potent than DFO (hexadentate) and 10 times more potent than deferiprone (bidentate). It is highly selective for iron and does not induce the excretion of zinc or copper. The principal observed toxicity of renal tubular epithelial cell damage has not occurred in iron loaded animals. As stated earlier, Fe(ICL 670)2 and ICL 670 itself are primarily excreted in the feces. This is in contrast to DFO where iron is excreted chiefly in the

![Fig. 1 : ICL 670 - iron complex.](image-url)
ICL 670 has been studied in phase-II,23,24 in a randomized double-blind placebo-control dose escalation study involving a total of 21 patients with ß-thalassaemia major. Patients were divided into 3 cohorts of 7 each. Five patients in each group received active drug while two received placebo. The first cohort received ICL 670 in dose of 10 mg/k/d. The second cohort received it in dose of 20 mg/k/d. The dose to be given to the third cohort was to depend on the interim analysis of the first two cohorts’ data. At the time of presentation in the 44th Annual ASH meeting, Philadelphia, December, 2002, 4/5 patients in the first cohort were already evaluable. They showed a net negative fecal iron balance of 9.2 ± 3.1 mg/d in comparison with two patients receiving placebo (0.07 ± 0.2 mg/d). The study, thus showed that ICL 670 could achieve substantial net negative iron balance. The study also estimated S. iron, total iron binding capacity (TIBC) and unbound iron binding capacity (UIBC) by atomic absorption spectroscopy. UIBC rose dramatically after ICL 670 confirming that the drug is capable of providing S. UIBC and thus probably protecting against iron-induced cardiac toxicity. The results from the second cohort on 20 mg/k/d were awaited. Patients were followed up in a metabolic unit and fed on a defined diet containing 10 mg Fe/2200 kcal.

Piga Antonio et al (Turin University in Italy)24 have studied and presented a study of 71 thalassaemic patients with transfusional iron overload. This was an open label, randomized, multicentre phase-II study to evaluate safety, tolerability and effects on liver iron concentration (LIC) of 12 months administration of ICL670 in doses of 10 mg/k/d and 20 mg/k/d v/s DFO 40 mg/k/d SC 5 days/week. LIC was measured by SQUID (Superconducting QUantum Interference Device, a method of measuring hepatic magnetic susceptibility) every 3 months. Results of LIC after 9 months of therapy were presented in the 44th Annual ASH meeting at Philadelphia, December, 2002 (Table 1).24 The mean reduction in liver iron content in the three groups, has been shown in Table-2.24

It was clear that ICL 670 is an extremely effective oral chelator which induced decrease in LIC similar to those achieved with standard doses of DFO. The suitability of once daily dosing for ICL 670 was also confirmed. Other than intermittent mild nausea, occasional abdominal pain and constipation at dose of 20 mg/k/d, the drug had no unmanageable toxicities and was well-tolerated. The encouraging results are provided the rationale for the ongoing phase III studies.

Studies have been carried out to assess the efficacy of DFO and ICL 670 in combination.22 The effect appears additive. One should not look upon any new iron chelator like ICL 670 as a compound displacing presently accepted and highly effective parenteral drug DFO. It should be used to extend the scope of iron chelating strategies in a manner analogous with the combined use of medications in the management of other conditions like hypertension and diabetes.25-27 Co-administration of oral chelator ICL 670 with injectable DFO would allow a decrease in doses of both the drugs improving compliance by decreasing the need for DFO administration. Combined use of DFO and L1 has already been shown to be effective and convenient in patients previously failing to single drug therapy.25,27 The combination may also have a “shuttle effect” i.e. ICL 670 working as an intracellular chelator and DFO as a powerful extracellular chelator,4,25,27

Besides these data on ICL 670, following research on chelation front has also been recently conducted but halted due to poor efficacy:

1) Development of “slow-release” depot formulation of DFO (Novartis). The research has been concluded due to inadequate efficacy.1,2

2) Development of “long-acting” hydroxyethyl starch-deferoxamine (Novartis). The results have been disappointing due to poor efficacy and further research has been halted.1,2

In addition, combination therapies have been looked upon as the most promising one. They are expected to produce synergistic effect leading to enhanced iron excretion from target specific iron compartments, less side-effects, improved compliance and individualization of therapy. Better kinetics of iron metabolism, iron overload and chelation would help in improving these innovative therapeutic strategies, some of which are

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients with LIC change (%)</th>
<th>Mean reduction in liver iron content (mg/g liver)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICL 670 (10 mg/k/d)</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>ICL 670 (20 mg/k/d)</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>DFO (40 mg/k/d)</td>
<td>1.2</td>
<td></td>
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</tbody>
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Table 3: Properties of iron chelating agents

<table>
<thead>
<tr>
<th>Feature</th>
<th>Deferoxamine (Desferal)</th>
<th>Deferiprone (Kelfer)</th>
<th>ICL 670 (Exjade)</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 I.V. infusion</td>
<td>Oral, 3 times a day</td>
<td>Oral, once a day</td>
</tr>
<tr>
<td>Tolerability</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>Unproven</td>
</tr>
</tbody>
</table>

enlisted below:

1) Combining pyridoxal isonicotinoyl hydrazone (PIH) analogs with DFO (Hershko Chaim et al).
2) Further studies on combination of DFO and Deferiprone.
3) Further studies on combination of Deferiprone and HBED.
4) Further studies on combination of DFO and 2,3-DHB.

During last two years, there has been significant work and publications on the efficacy of ICL 670 as an iron chelator in patients of transfusional iron overload especially thalassaemia. Table 3 summarizes the properties of three most effective iron chelating agents.

In conclusion, based on the studies mentioned above, it appears that ICL 670, an oral iron chelator has good tolerance and it is at least as effective as DFO in promoting a negative iron balance and decreasing liver iron concentration in patients with iron overload.

References


25. Grady RW, Berdoukas V, Rachmilewitz EA, et al. When deferiprone and desferrioxamine are combined, iron excretion is enhanced. Abstract No. 2060, 44th Annual ASH meeting,


30. BerlinerN, Rose M. Novel oral chelator ICL 670 is as effective as deferoxamine in promoting iron elimination in patients with thalassaemia (ASH-online, in press).


