Thalassemia, myelodysplastic syndrome (MDS) and sickle cell disease (SCD), long-term substitution therapy for anemia results in toxic iron overload which constitutes a significant medical problem. As humans have no physiological mechanism to excrete excess iron, this is deposited in the form of ferritin and hemosiderin in the liver, spleen, many endocrine organs and in the myocardium. This accumulation results in a host of clinical complications such as heart disease, diabetes, hypothyroidism and liver failure, and the primary causes of death among patients who require regular transfusions are due to the effects of iron overload rather than the underlying problem.

Treatment options for iron overload are limited. Currently, two iron-chelating agents are licensed for the treatment of iron overload: deferoxamine and deferiprone. More than 35 years of clinical experience with deferoxamine (Desferal®) has established that chelation therapy in thalassemia patients with iron overload reduces related pathologies, normalizes growth, prevents cardiac insufficiency and improves patients’ quality of life.1,2

The poor oral bioavailability and a short plasma half-life of deferoxamine (DFO), however, require parenteral administration and a slow infusion time. The inconvenient route of administration and associated complications mean that compliance with life-long therapy is a significant issue. As a consequence, many patients are believed to die unnecessarily due to poor maintenance therapy.1,4

Although deferoxamine has clearly established the value of iron chelation in avoiding the serious complications of iron overload, poor patient compliance can significantly limit therapeutic success. Deferiprone (L1; Ferriprox®, Apotex) (DFP) is a bidentate, orally active iron chelator, registered in some countries, which is formulated as solid tablets and administered three times a day. Prospective clinical data documenting the efficacy of deferiprone are limited.5,6 In addition, its therapeutic window is narrow, and its safety risks include drug-related agranulocytosis and arthropathy.7 In Europe use of deferiprone is restricted to β-thalassemia major patients who cannot adequately be treated with deferoxamine, with weekly monitoring of the complete blood cell count. The safety and efficacy of deferiprone have not been well studied in children less than 6 years of age, even though such pediatric patients also have increased iron stores. Comparisons of the effects of DFP and DFO are largely based on retrospective analyses,8 and large well-designed prospective studies of this agent are required to clarify the comparative effects of these agents.

ICL670: a novel oral iron chelator

ICL670 (Deferasirox) is a once-daily oral chelator developed specifically for the treatment of chronic iron overload. It represents a new class of tridentate iron chelators with a high specificity for iron.9 Efficient and selective mobilization of tissue iron has been demonstrated in several animal models, with efficiency being greater than deferoxamine, and considerably greater than deferiprone.10

ICL670: clinical outcome

A robust clinical programme has been developed to establish the safety and efficacy of once-daily oral ICL670 (Table 1). Phase I clinical evaluation of ICL670 has shown this novel agent to be well tolerated, with no safety concerns at doses up to 80 mg/kg/day. Dose-dependent iron excretion was achieved (almost entirely in the feces), and averaged approximately 0.127, 0.344 and 0.564 mg/kg/day at the 10, 20 and 40 mg/kg doses, respectively. The plasma half-life (11–19 hours) supports the once-daily oral dosing regimen used in subsequent clinical evaluation.11,12 Exposure (area under the plasma concentration curve, AUC 0–24h) and the maximum plasma concentration (Cmax) increased nearly proportionally with the dose.
A positive trend towards increased amounts of iron excreted in the urine was observed when the AUC 0-24h of ICL670 and the iron complex exceeded specific threshold values at the 40 and 80 mg/Kg dose levels.11 A dose escalation study has been undertaken in patients with β-thalassemia in order to assess safety and tolerability, pharmacokinetics and cumulative net iron excretion (NIE, measured by faecal and urine output). A randomized, double blind, placebo-controlled design was utilized with doses of 10, 20 and 40 mg/Kg being administered daily for a period of 12 days. A linear relation was recorded between exposure to ICL670 and total iron excretion. All 3 doses resulted in a positive NIE, and the NIE achieved at the mid-dose of 20 mg/Kg/day was noted as being able to prevent net iron accumulation in most patients transfused with 12-15 ml packed red blood cells/Kg/day (Figure 1). In a phase II study the tolerability of ICL670 in comparison with deferoxamine has been determined in 71 patients with transfusional hemosiderosis.

Patients were randomized to receive ICL670 (10 or 20 mg/kg day p.o.; n=24 in both groups) or deferoxamine (40 mg/kg sc on 5 days per week; n=23). The incidence of adverse events was similar in all groups. Decreases in LIC (as determined by non-invasive biomagnetic susceptometry, SQUID) were of a similar magnitude in the ICL670 20 mg/kg and deferoxamine groups, with LIC values at baseline of 8.5 and 7.9 mg/g dw respectively, falling to 6.6 and 5.9 mg/g dw at 48 weeks. The pharmacokinetics of ICL670 allow once-daily administration with a rapid increase in serum concentration after administration and an elimination half-life of 8-16 hours.13 A multinational Phase III randomized trial comparing ICL670 to deferoxamine over one year was initiated in pediatric and adult patients with β-thalassemia receiving regular blood transfusions in order to further evaluate its efficacy in body...
iron reduction. β-thalassemia was selected as the model disease for demonstration of efficacy across the range of patients at risk of iron overload.

Patients were randomized and received treatment with ICL67 (n=296) or deferoxamine (n=290) with dosing of each agent according to baseline liver iron concentration (LIC) as determined by analysis of liver biopsy specimens in 84% of patients. The primary endpoint was maintenance or reduction of LIC; secondary endpoints included safety and tolerability, change in serum ferritin level and net body iron balance. In both arms patients with LIC values ≥7 mg Fe/g dw had similar reductions in LIC, similar changes in serum ferritin, and similar net body iron balance. Due to protocol design, patients with lower LIC values received proportionally lower doses of ICL670 relative to deferoxamine compared to patients with higher LIC values, and this resulted in the primary endpoint not being met in the overall population of patients (Figure 2).

The most common adverse events included rash, gastrointestinal disturbances, and mild non-progressive increases in serum creatinine. No agranulocytosis, arthropathy or growth failure was associated with deferasirox administration.16 In the setting of mielodysplastic patients (MDS), where transfusional burden is generally less than that of β-thalassemia, ICL670 has shown high efficacy in trials at doses of 10 mg/Kg/day and above.16 ICL670 (Deferasirox) is a promising once-daily oral therapy for the treatment of patients with transfusional iron overload.

References