Drugs of the Future 2005, 30(12): 1241-1251

CCC: 0377-8282/2005
DOI: 10.1358/dof.2005.030.11.942323

Review Article

New oral iron-chelating drugs for the treatment of transfusional iron overload and other diseases

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CONTENTS

Abstract

Iron chelation therapy has improved dramatically with the introduction of deferiprone (L1) more than 10 years ago. In particular, selective deferiprone/deferoxamine combination therapy protocols appear to be universally effective in the treatment of iron overload. New chelators have also been developed, some of which are under clinical evaluation, such as deferasirox (ICL-670; Exjade), deferitrin (GT-56-252), L1NAll and starch deferoxamine polymers. ICL-670 has recently been approved by the U.S. FDA under the accelerated approval regulations with postmarketing surveillance requirements for up to 2012. It is effective in reducing liver iron but is generally ineffective in causing negative iron balance or reducing cardiac iron. ICL-670 and the other experimental iron chelating drugs have no major advantages in efficacy and toxicity in comparison to deferiprone, deferoxamine or their combination. It is likely that the new experimental iron chelating drugs will be used in combination therapies with deferiprone, deferoxamine and possibly other chelators for improving existing therapies. A major setback of these new drugs is that their cost will be prohibitive for the vast majority of thalassaemia patients living in developing countries. In contrast, the price of deferiprone is likely to be reduced because one of its major patents is due to expire.

Introduction

Iron overload is the most common chronic metal toxicity condition and is associated with the highest morbidity and mortality rate worldwide. It can be caused by increased gastrointestinal iron absorption (primary siderosis) or regular transfusions of red blood cells (secondary siderosis), or a combination of both processes (1). β-Thalassemia and idiopathic hemochromatosis are the most common inherited disorders associated with iron overload and toxicity. In idiopathic hemochromatosis, the genetic abnormality is related to a mechanism of increased gastrointestinal iron absorption and the condition is treated with venesection (1, 2). In β-thalassemia, there is insufficient or no production of the β-chain of hemoglobin, leading to the production of abnormal, nonfunctional hemoglobin and red blood cells, resulting in severe anemia (3). The treatment of β-thalassemia patients is based on regular red blood cell transfusions and almost daily iron chelation therapy in order to remove the excess iron accumulating in the body from the catabolism of hemoglobin of senescent red blood cells (1).

It is estimated that more than 100,000 babies are born with thalassemia annually from about 100 million asymptomatic thalassemia heterozygote carrier parents worldwide. More than 80% of thalassemia patients live in the Middle East and Southeast Asia and the remaining mainly in the Mediterranean area (3, 4). There are many other conditions where red blood cell transfusions are used regularly and lead to iron overload, such as sickle cell anemia, myelodysplasia, aplastic anemia, sideroblastic anemia, Blackfan-Diamond anemia, Fanconi's anemia, renal dialysis, cancer, etc. (Table I) (1).

Chelating drugs for the treatment of transfusional iron overload are listed in the orphan drug category in Western Europe and North America because of the small number of patients by comparison to the total population, which is mainly of Caucasian descent (5).

Most of the excess iron derived from red blood cell transfusions is stored in the liver and spleen, but also in the heart, pancreas and other organs. Regularly transfused patients, and especially thalassemia patients, not receiving effective chelation therapy usually die from congestive cardiac failure caused by iron overload toxicity.

Table I: The use of iron chelators in the treatment of iron overload and the prospect of future applications in other diseases.

Iron overload conditions

- β-Thalassemia major
- β-Thalassemia intermedia
- HbE/β-thalassemia
- HbS/β-thalassemia
- Sickle cell anemia
- Aplastic anemia
- Sideroblastic anemia
- Pyruvate kinase deficiency
- Blackfan-Diamond anemia
- Fanconi's anemia
- Congenital atransferrinemia
- Hereditary hypochromic anemia

- Hemolytic disease of the newborn
- Idiopathic hemochromatosis
- Iron overload in liver disease
- Iron overload in hemodialysis
- Prophyria cutanea tarda
- Dietary or latrogenic iron intake
- Iron poisoning

Iron imbalance conditions

- Iron deficiency anemia
- Anemia of chronic disease
- Friedreich's ataxia
- Hallevorden-Spatz syndrome

Other metal toxicity conditions

- Aluminium overload in renal dialysis or in accidental poisoning
- Wilson's disease (copper overload)
- Plutonium contamination and toxicity
- Uranium contamination and toxicity
- Indium overload
- Gallium overload

Neoplastic and other diseases

- Neuroblastoma
- Various forms of cancer
- AIDS
- Microbial infections
- Malaria and other parasitic infections

Other conditions/uses

- Conditions of free radical damage
- Cyclooxygenase and lipoxygenase inhibition
- Drug toxicity, *e.g.*, prevention of cardiac toxicity by doxorubicin
- Ischemia-reperfusion injury
- Storage of organs for transplantation
- Alzheimer's disease
- Parkinson's disease
- Rheumatoid arthritis
- Metal imbalance conditions
- Radiopharmaceutical
- Diagnostic medicine
- Magnetic resonance imaging

This form of toxicity causes serious damage to major organs, including the heart, pancreas, endocrine organs, etc. (6). The early introduction of chelation therapy and its regular effective use can increase the life span of transfusional iron-loaded patients. The life span of regularly transfused thalassemia patients not receiving chelation therapy is about 20 years maximum. In contrast, some thalassemia patients in developed countries who have received chelation therapy since their early childhood have exceeded the age of 50 years. Thus, effective chelation therapy has transformed β-thalassemia from a fatal to a chronic disease, despite the fact that thalassemia patients may experience many other clinical complications and other treatments during their life time.

The rate of red blood cell transfusions in beta-thalassemia and other transfusion-dependent conditions is aimed at maintaining hemoglobin levels at about 110-120 g/l. This usually requires the transfusion, at regular intervals of about 2-4 weeks, of 1-3 units, each containing 200-250 ml of packed red blood cells, equivalent to about 200-250 mg of iron per unit. This rate of transfusion causes a net excess iron deposition in the body of about 15-20 mg/day, which is the target amount of iron removal by chelation therapy.

There are numerous methods for estimating excess body and organ iron load, as well as the efficacy of iron chelation therapy, in transfused iron-loaded patients. The most common and indirect parameters for estimating body iron levels are serum ferritin, transferrin iron saturation and urinary iron excretion in response to iron-chelating drugs such as deferoxamine and deferiprone. A more accurate but invasive method of liver iron estimation is the determination of iron concentration and the histopathological assessment of iron deposits in liver biopsies (1).

New noninvasive methods have recently been developed and are gaining ground in the diagnosis of iron over-

load. One of these is SQUID-biosusceptometry, which is used for liver iron estimation and correlates well with results from liver biopsies (7, 8). The magnetic resonance imaging (MRI) techniques T2 and T2* are also increasingly important and powerful tools for assessing differential organ iron deposition, and in particular cardiac iron load, which is critical for the prognosis of iron-loaded patients (9, 10). Another indirect parameter for assessing potential iron toxicity rather than iron overload is non-transferrin-bound iron (NTBI), which usually appears in plasma when transferrin is fully saturated with iron (11). All the above methods are used periodically for assessing the iron load of patients. They are also used for adjustments in chelation therapy and for choosing the appropriate monotherapy or combination therapy dose protocols. The same diagnostic methods are also used for identifying promising experimental iron-chelating drugs intended for clinical use.

A major problem in the treatment of thalassemia is the cost of chelation therapy, which is estimated at USD 5-10 thousand per year per patient receiving deferoxamine. This cost is prohibitive for the vast majority of thalassemia patients who live in developing countries (12). The oral chelating drug deferiprone is less expensive than deferoxamine and it can be provided at about USD 0.5 thousand per year per patient. The overall global annual sales of iron-chelating drugs are estimated at USD 1 billion. The size of this lucrative drug market is the major incentive for multinational pharmaceutical companies to become involved in the development of new chelating drugs, especially since the patent on deferoxamine has expired and that of deferiprone will expire in 2008.

The selection of an ideal iron-chelating monotherapy or combination therapy for worldwide use in regularly transfused patients is usually based on properties such as iron removal ability following oral administration, effectiveness in achieving and maintaining negative iron balance, low and acceptable toxicity, and low cost. Hundreds of chelators have been designed and tested *in vitro* and *in vivo* in the last 50 years for the treatment of thalassemia and other transfusional iron overload conditions (1, 13, 14). However, only about 20 reached the stage of clinical trials and, with the exception of a few, most have been abandoned either because of toxicity or lack of efficacy in iron removal, or due to financial assessments and other considerations by pharmaceutical companies (1, 14).

Deferoxamine and deferiprone (Fig. 1) are the only approved and widely used iron-chelating drugs at present. New experimental chelating drugs are currently undergoing clinical evaluation and are expected to become available in the near future. The new chelating drugs, however, have not so far been shown to have any major advantages over deferiprone, deferoxamine or their combination. The overall selection criteria for the use of one chelating drug or a combination of chelating drugs in any country is usually based on a risk/benefit assessment, as well as the cost of treatment. The latter is of crucial importance for patients living in developing countries.

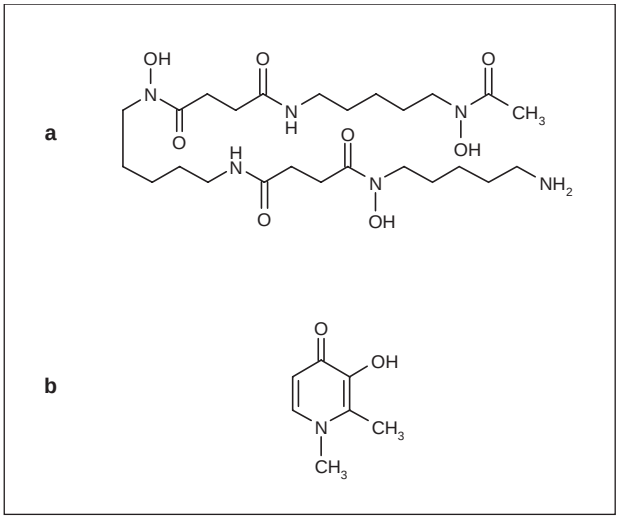

Fig. 1. Chemical structures of the iron-chelating drugs deferoxamine (a) and deferiprone (b).

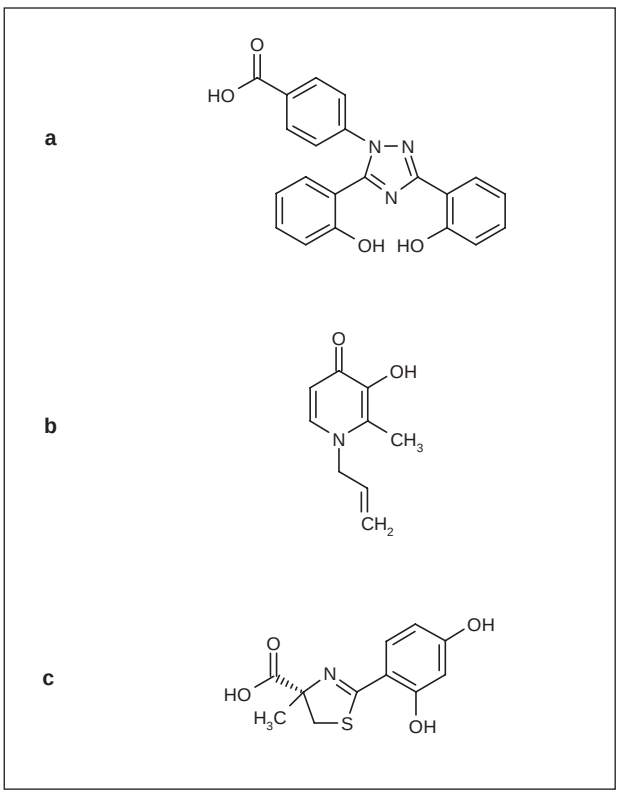

Fig. 2. Chemical structures of the experimental iron-chelating drugs deferasirox (a), L1NAll (b) and deferitrin (c).

There are at least five iron chelators that have reached the stage of clinical testing and are currently being developed for clinical use (Fig. 2). One of these is a deferiprone derivative, namely, 1-allyl-2-methyl-3-hydroxypyrid-4-one (L1NAll), which has reached phase I clinical testing. Similarly, two different deferoxamine starch polymers, which are administered intravenously

(i.v.), have also been tested in phase I clinical trials. Two other structurally related chelators, namely ICL-670 (deferasirox) and GT-56-252 (deferitrin), have reached phase III and phase II clinical testing, respectively.

The overall results for all five experimental chelators appear so far to be promising but not significantly better in terms of efficacy and toxicity by comparison to the established drugs deferiprone and deferoxamine or their combination. It is therefore likely that future chelation treatments will be based on chelator combinations rather than monotherapies. It is also likely that these and other chelating drugs will be used in the treatment of other conditions in addition to iron overload (Table I) (1).

Iron chelation therapy using deferoxamine, deferiprone and their combination

The established iron chelation therapy for thalassemia and other transfused patients using deferoxamine, deferiprone or their combination is considered to be effective, safe and satisfactory for the vast majority of patients who have access to them. Deferoxamine is used as the first-line treatment in developed countries, but deferiprone is also increasingly used in many patients in the E.U. and other developed countries because of the high cost of and complications associated with deferoxamine treatment. In India, for example, more patients are using deferiprone than deferoxamine. In the last few years, increasing numbers of patients are using deferiprone and deferoxamine combination therapies with very promising results. In Cyprus, for example, it is thought that more patients are using combination therapies than either monotherapy. The general characteristics of the established treatments are described below.

Iron chelation therapy using deferoxamine

The introduction of deferoxamine in the mid-sixties resulted in a decrease in the morbidity rate and in an overall increase in the survival of thalassemia patients (15). Deferoxamine is effective in maintaining negative iron balance in most patients if it is injected intravenously (i.v.), or more commonly subcutaneously (s.c.) over 8-24 h/day at a dose of 40-60 mg/kg with the aid of an electronic pump or a 24-h infusor at least 5 days per week (6).

However, there are several drawbacks associated with the use of deferoxamine, mainly its lack of activity upon oral administration and the need to be administered as a prolonged s.c. infusion to be effective, which leads to low compliance in most patients. Deferoxamine is also very expensive and therefore not available to the majority of thalassemia patients in developing countries. Additionally, there are many toxic side effects associated with the deferoxamine treatment. The most common non-serious toxic side effects are related to the development of hardness and swelling at the injection site after s.c. and i.v. administration. Other toxic side effects, such as ocular, auditory and bone abnormalities, are more serious but less common and usually occur in patients with low iron stores receiving high doses of deferoxamine (> 50-60 mg/kg) (1).

There is very limited information regarding the pharmacokinetic and metabolic properties of deferoxamine. Several preliminary studies have shown that deferoxamine is rapidly cleared from blood with a half-life of 5-10 min and with a rate faster than its iron complex (half-life approximately 90 min). It is metabolized to a number of metabolites, some of which are known to have iron-chelating properties (15, 16). There is variation in the metabolism and level of iron excretion among iron-loaded patients treated with deferoxamine. The increase in iron excretion induced by deferoxamine is mainly observed in the urine, and to a lesser extent in the feces.

Insufficient chelation due to low compliance, which leads to cardiomyopathy, is considered the main cause of death in thalassemia patients treated with deferoxamine in developed countries such as the U.K., where the mean life span was estimated at 35 years (17). In contrast, in developing countries, the main cause of mortality in transfused thalassemia patients is insufficient chelation therapy due to the high cost and lack of availability of deferoxamine (12).

Iron chelation therapy using deferiprone

Deferiprone was designed in 1981 at the Department of Chemistry of the University of Essex in the U.K. (18). It has since been tested in many *in vitro* and *in vivo* models of iron mobilization and toxicity (14, 18). The first clinical trials in transfusional iron-loaded patients using deferiprone were reported in 1987 and indicated that it had high efficacy in increasing iron excretion and low toxicity (19, 20). Deferiprone was first approved in India in 1994 and launched under the commercial name Kelfer by CIPLA, and subsequently in Europe in 1999 under the commercial name Ferriprox by the Canadian company Apotex. It is estimated that since 1987 deferiprone has been used by more than 15,000 patients in over 50 countries either as monotherapy or in combination with deferoxamine (14).

Deferiprone is administered to patients as a tablet or a capsule and is rapidly absorbed, mainly from the stomach, appearing in blood within minutes (21, 22). In iron-loaded patients it is partly metabolized to a glucuronide conjugate that has no iron-chelating properties, and it is cleared from blood mainly in the form of a glucuronide conjugate and a deferiprone-iron complex. The plasma half-life of the deferiprone/deferiprone-iron complex is 47-134 min. Deferiprone, its iron complex and its glucuronide conjugate are all excreted in the urine (22-24). There are variations among patients in relation to the rates of absorption, glucuronidation and clearance of deferiprone, as well as in the clearance of its glucuronide metabolite and iron complex (25). The level of urinary iron excretion caused by deferiprone is generally related to the iron load of the patients and the dose of deferiprone.

Iron mobilization from iron-loaded patients treated with deferiprone, similar to deferoxamine, appears to be partly via NTBI circulating in plasma. Transferrin-bound

iron has also been shown to be mobilized in thalassemia patients, usually when the plasma deferiprone concentration exceeds 100-200 μM (22, 26, 27). Iron mobilization from excess iron deposits stored in the liver and the heart in the form of ferritin and hemosiderin has been shown during long-term chelation therapy with deferiprone. Depletion of liver iron in iron-loaded patients taking deferiprone at doses of at least 75 mg/kg/day has been confirmed repeatedly by liver biopsies and SQUID-biosusceptometry monitoring (28, 29). Studies using MRI T2 and T2* relaxation time measurements have shown that deferiprone is more effective than s.c. deferoxamine in the removal of iron from the heart of iron-loaded thalassemia patients (30-33). The difference in cardiac iron removal between deferiprone and deferoxamine appears to be related to their different mechanisms of iron chelation, as well as their physicochemical and pharmacological properties (1, 14, 30-33).

The use of doses of 75-120 mg/kg/day of deferiprone is in most cases sufficient to produce a negative iron balance in iron-loaded thalassemia patients (19, 28, 29, 34-36). More intensive chelation therapy protocols of deferiprone can also be used and doses up to a total of 250 mg/kg/day have been shown to cause continuous increases in iron excretion of up to 325 mg/day in thalassemia patients (26).

Several toxic side effects have been reported during the use of deferiprone in the last 18 years, all of which are controllable, manageable and reversible (1). About 5% of patients may discontinue deferiprone therapy due to toxicity. It is estimated that arthropathy or joint/musculoskeletal pain can affect up to about 10% of patients, zinc deficiency 1%, gastrointestinal complaints 6%, neutropenia 5% and agranulocytosis, which is the most serious toxic side effect of deferiprone, < 0.6% (1, 37-39). As a result of agranulocytosis, prophylactic weekly or fortnightly blood counts are mandatory for monitoring the neutrophil count of patients treated with deferiprone.

Iron chelation therapy using deferiprone and deferoxamine combinations

The combination of deferiprone and deferoxamine was originally suggested more than a decade ago for patients who were experiencing toxicity or had low iron excretion in response to either iron chelator alone, or due to low compliance with s.c. deferoxamine therapy (40). The combination is now widely used and increasing numbers of thalassemia patients are being treated with the combination compared to either monotherapy (1, 40-43). Combination therapy is mainly used to increase the compliance of thalassemia patients by reducing the number of daily administrations per week of s.c. deferoxamine. It is also used to decrease the toxicity experienced by either deferiprone or deferoxamine, because of the possibility of using lower doses of the drugs in combination. It can also be used for increasing iron excretion because of the administration of higher overall chelator doses compared to either of the monotherapies (11, 40-43).

The selection of the dose protocol, and to a lesser degree other factors, can influence the efficacy and toxicity of combination therapy with deferiprone and deferoxamine (1). Different dose protocols can be used in patients to target the removal of iron from specific organs such as the heart, maintain a negative iron balance, reduce chelating drug toxicity, or all of the above. Within this context, the combination therapy protocol will be different for each patient (40-43).

The combination therapy protocol suggested by the International Committee on Oral Chelators (ICOC), involving the administration of deferiprone during the day at 80-110 mg/kg/day and of s.c. or i.v. deferoxamine at least 3 times per week at 40-60 mg/kg during the night, appears to be universally effective for the treatment of regularly transfused iron-loaded patients. The ICOC protocol appears to cause the rapid and safe removal of excess iron from the heart, usually within 1 year, and also to bring and maintain iron-loaded thalassemia patients into negative iron balance (44).

The selection of a dose protocol may affect the iron chelation mechanism of the combination therapy, which may involve a synergistic and or an additive chelation effect between deferiprone and deferoxamine. As a result of this mechanism, the continuous mobilization of storage and plasma iron pools, as well as the prevention of iron accumulation in organs, can be facilitated. The latter is accomplished by the efficient mobilization of iron from NTBI and transferrin, both of which are implicated in the transport of iron in plasma and its deposition in various tissues. Iron accumulated in various tissues is mainly derived from iron released in plasma by the reticuloendothelial system following the breakdown of senescent red blood cells and the catabolism of hemoglobin (1).

Deferiprone/deferoxamine combination therapy offers the possibility in many transfused iron-loaded patients of a more effective and also less toxic chelation therapy compared to either monotherapy. The choice of chelation monotherapy or combination therapy will increase in the future with the introduction of new chelating drugs, which, due to differences in their mode of action, can be targeted for iron removal from specific organs or for other effects when used as monotherapy or in combinations with other chelating drugs. The new chelation therapies may increase the efficiency of iron removal and decrease the toxicity compared to existing monotherapies in iron-loaded patients. They may also offer the opportunity for a wider choice of treatment and applications that can benefit both patients with transfusional iron overload and patients with many other iron- and non-iron-loading conditions where iron-chelating drugs may also play a role (1, 44, 45).

Experimental iron-chelating drugs undergoing clinical evaluation

Deferasirox

Deferasirox (ICL-670, Exjade; Fig. 2) is a bis-hydroxyphenyltriazole benzoic acid derivative developed by

Novartis for the treatment of transfusional iron overload (46, 47). It is a lipophilic, charged tridentate iron chelator, forming a charged iron complex with a molar ratio of chelator to iron of 2:1 at physiological pH.

There is limited published information regarding the pharmacological and toxicological effects of deferasirox, but several of its pharmacological and other characteristics are not typical of other chelating drugs. In a number of studies, deferasirox has been shown to be effective at reducing excess liver iron in iron-loaded animals and patients. In contrast to deferiprone and deferoxamine, it has been shown to increase fecal but not urinary iron excretion in iron-loaded thalassemia patients (46-48).

Clinical trials in iron-loaded thalassemia patients have shown that doses of 10, 20 and 40 mg/kg of deferasirox can cause a net increase in iron excretion. However, the level of iron excretion was not sufficient to cause negative iron balance (> 15-20 mg iron) in the majority of patients at the dose of 20 mg/kg. At 40 mg/kg, the mean iron excretion increased to 23 mg/day/50 kg, which, however, was still lower than that achieved by deferiprone, where doses of 75 and 100 mg/kg have been shown to produce a mean iron excretion of 27 and 42 mg/day, respectively (48, 49). Similar results were obtained in a subsequent study of 6 months' duration, where iron excretion caused by deferasirox in most patients was 7.7-28.5 mg/day (46).

In initial clinical trials, deferasirox was shown to have a slow rate of plasma clearance, with a half-life of 12-16 h (48). This slow clearance reduces the possibility of repeated daily administration and therefore the prospect for further increases in iron excretion (49).

In subsequent studies, deferasirox was shown to be rapidly absorbed following oral administration, reaching peak plasma concentrations at 1-3 h, with an elimination half-life of about 19 ± 6.5 h for the doses mostly used for long-term therapy in patients, *i.e.*, 20 and 30 mg/kg. The iron complex of deferasirox has been shown to have a longer plasma half-life than deferasirox (50). A slower rate of clearance from plasma was also previously observed for the deferiprone-iron complex in pharmacokinetic studies in thalassemia patients treated with deferiprone. This difference may be due to the larger size of the iron complex of deferiprone compared to the smaller size of non-iron-bound deferiprone (22). In contrast to the urinary route of iron excretion observed in the case of the iron complexes of deferoxamine and deferiprone, the excretion of the deferasirox-iron complex was entirely in the feces via the bile. This difference may be related to the much larger molecular weight of the deferasirox-iron complex, which does not appear to facilitate clearance from the kidneys, compared to the much lower molecular weight iron complexes of deferaxamine and deferiprone (51).

There is still a lot of controversy with regard to the mode of action and toxicity of deferasirox (45, 49). For example, not only has iron removal from organs other than the liver not yet been shown in iron-loaded animals and patients, but it is suspected that the lipophilicity of the iron complex may actually cause the transfer of iron from the plasma into other organs, *e.g.*, the heart, directly or via donation of iron to transferrin (45, 49, 52, 53). Similarly, the possibility of deferasirox and its iron complex crossing the blood-brain barrier due to their high lipophilicity is another major toxicity issue that needs to be investigated. The ability of deferasirox to increase the absorption of dietary iron or other metals, similar to other lipophilic chelators, also needs to be clarified (49, 54).

Although no information on the metabolism of deferasirox is available, the pharmacokinetic and ferrokinetic data on deferasirox strongly support the presence of metabolite(s), some of which may have iron-chelating properties and may also be involved in the toxic side effects of the drug (49, 51).

The long-term efficacy and toxicity of deferasirox are currently under investigation. More than 1,000 patients have received the drug in the past 3 years. In 1-year clinical trials with deferasirox involving more than 800 patients in several countries and with different transfusional iron-loading conditions, including thalassemia, myelodysplasia and sickle cell anemia, it was reported that deferesirox was not as effective as deferoxamine in reducing liver iron and serum ferritin levels (55-57). However, despite this finding, the difference between deferasirox and deferoxamine may be underestimated and cannot yet be clearly evaluated unless the compliance of the patients treated with s.c. deferoxamine is clearly defined. It is well recognized that only a small percentage of patients can comply with the 5-days-per-week dose protocol of s.c. deferoxamine used for comparison in the 1-year study. Concerns were also expressed regarding the monitoring of other aspects of the efficacy and toxicity of deferasirox, in particular the iron status and function of the heart (51). It should be noted that iron removal from the heart and improvement in cardiac function have been reported in a 1-year study using i.v. deferoxamine, while no such findings have yet been reported for deferasirox (58).

Information on the toxicity of deferasirox is not yet fully or readily available. The toxic side effects reported so far for deferasirox include skin rash, gastrointestinal symptoms (nausea, vomiting, diarrhea and abdominal pain), increases in transaminases and creatinine in 33% of the patients (46, 55-57). It is not known whether these toxic side effects are related to deferasirox or its metabolite(s) (51). The dropout rate for patients treated with deferasirox is estimated to be 3-10% (45).

The future prospects for the use of deferasirox will depend on the results of further studies and information regarding its long-term efficacy and toxicity. In the absence of any evidence of beneficial effects on the heart, it is unlikely that deferasirox can be used as an effective monotherapy for thalassemia and other transfused iron-loaded patients. Combination therapy with deferiprone and deferoxamine may overcome many of the difficulties associated with deferasirox therapy. For example, deferiprone and deferoxamine may remove iron from the "floating" deferasirox-iron complex in plasma, causing its rapid excretion in the urine. However, there

are also several advantages to the use of deferasirox. For example, its low dose may be associated with an increase in compliance and a lower cost of treatment, especially for thalassaemia patients in developing countries. Its use may also be beneficial in the treatment of patients experiencing toxicity and iron removal complications with deferiprone, deferoxamine or their combination (45, 49, 51).

Despite the concerns regarding the use of deferasirox and the possible drawbacks, Novartis announced that the overall results gathered so far were sufficient for a global filing application, which was submitted in 2005 in the U.S. and the E.U. for the treatment of iron overload in regularly transfused patients.

Deferitrin

Deferitrin (GT-56-252; Fig. 2) is a desferrithiocin analogue developed by Bergeron *et al.* and Genzyme Corp. (59-61). Deferitrin is a charged tridentate chelator forming a charged complex with a molar ratio of chelator to iron of of 2:1 at physiological pH. There is limited information on the pharmacological and other properties of deferitrin, which is currently undergoing phase II clinical trials. Animal studies and preliminary clinical trials in iron-loaded thalassemia patients have shown that it is effective in increasing iron excretion.

Studies in primates have demonstrated that deferitrin at a dose of 75-150 μmol/kg can induce an increase in iron excretion, with an iron removal efficiency of about 13.5-17.5% (59). In pharmacokinetic studies in rats, dogs and monkeys using [^{14}C]-labeled drug, deferitrin at 30-60 mg/kg proved to be orally effective and was rapidly absorbed within 0.5-1 h after oral administration. It was also distributed throughout the body and eliminated with a half-life of 3-8 h. Further studies carried out in fasting and nonfasting animals have shown that food can inhibit the absorption of deferitrin. Iron excretion in rats and dogs was predominantly via the urine (80%), with less in the feces (20%). Some of the iron complex of deferitrin was detected in the plasma several hours following the administration of the drug (60).

The “floating” deferitrin-iron complex in plasma is similar to that observed with deferasirox, and in both cases appears to be related to the high molecular weight of the iron complexes (45). Combination therapy with deferiprone may facilitate the clearance of iron from the iron complex of deferitrin “floating” in plasma and may increase urinary iron excretion, similar to combination therapy with deferiprone and deferasirox.

In phase I clinical trials in 18 thalassemia patients, deferitrin at doses of 3-8 mg/kg was found to be well absorbed and well tolerated, without serious toxicity (61). Phase II clinical trials, including iron balance studies, are currently in progress. Preliminary indications suggest that deferitrin is unlikely to be sufficiently effective for use as monotherapy in transfusional iron overload, but that it may be beneficial in combination with deferiprone, deferoxamine and possibly other chelating drugs approved in the future.

1-Allyl-2-methyl-3-hydroxypyrid-4-one

1-Allyl-2-methyl-3-hydroxypyrid-4-one, or L1NAll (Fig. 2), is a second-generation α-ketohydroxypyridine iron chelator and a deferiprone analogue. Its preparation is simple and inexpensive, similar to deferiprone, and involves one synthetic step: the reaction between maltol and allylamine (62-64). L1NAll is a neutral molecule forming a neutral iron complex with a molar ratio of chelator to iron of 3:1 at physiological pH. It is more lipophilic than deferiprone. It has high specificity for iron, but can also form strong complexes with Al and Cu. It is generally more effective than deferiprone in removing iron from iron-loaded animals (65-67).

In vitro studies have shown that L1NAll is effective in mobilizing iron from transferrin, ferritin and hemosiderin at levels similar to deferiprone. It has also been shown to cause much higher levels of iron excretion compared to deferiprone and deferoxamine in iron-loaded mice, rats and rabbits (65, 66). In iron metabolic studies in rabbits, iron excretion with L1NAll was estimated to be 50-65% in the feces, with the rest in the urine. L1NAll has also been shown to cause a decrease in iron absorption in mice compared to non-chelator-treated control animals. The decrease in the level of iron absorption was less than that with deferiprone but higher than that with deferoxamine (66).

In acute toxicity studies with L1NAll in normal mice, the median lethal dose of intragastrically administered drug was in the range of 800-900 mg/kg, whereas that of intraperitoneally administered drug was 300-400 mg/kg. In contrast to normal rats, much lower acute, subacute and chronic toxicity was observed in iron-loaded rats using the same doses, suggesting that iron binding offers protection against L1NAll toxicity and also that some of the toxic side effects may be related to its high iron removal efficacy from metabolic pathways involving iron (66, 67).

A number of studies have shown that L1NAll has other pharmacological effects in addition to iron chelation. For example, it has been shown to have bactericidal activity against *Salmonella typhimurium* and other bacterial strains. Neither the chelator nor its iron complex appears to have mutagenic properties (68). Results from *in vitro* and *in vivo* experimental models also suggested that L1NAll can act as an effective antioxidant and that it can remove toxic metals such as Al and Ga from rats (69).

In a preliminary phase I study in healthy volunteers using doses of up to 1.5 g, L1NAll was well tolerated and further studies are in progress.

Starch deferoxamine polymers for intravenous administration

Starch deferoxamine polymers are apparently being developed for clinical use. The principal idea was that i.v. administration of these deferoxamine derivatives would result in a longer plasma half-life, higher iron-binding capacity and higher iron excretion that deferoxamine. Two of these starch deferoxamine polymers were pre-

Table II: Summary of the postmarketing studies needed to describe and verify clinical benefit by ICL-670 (Exjade).

Studies that are a condition of the accelerated approval of ICL-670 (Exjade).
Assessment of iron concentration and cardiac function in patients treated with ICL-670 (Exjade).
Continuation for another 4 years of the comparative studies with deferoxamine in various transfusional iron loading conditions.
A study in patients with congenital or acquired anemias and chronic iron overload.
Completion of studies regarding safety and efficacy in sickle cell disease.
A 5-year study in 200 patients of 2-6 years to study growth, development and toxicity.
Studies that are not a condition of the accelerated approval of ICL-670 (Exjade).
A 3-year follow-up study to collect safety and efficacy data in patients with elevated baseline serum creatinine.
A single-dose pharmacokinetic study in subjects with hepatic impairment.
A drug-drug interaction study.
A 3-year follow-up in 150 patients with myelodysplastic syndromes to evaluate safety (including cardiac, hepatic, endocrine and renal), hematological and clinical benefit.
Ophthalmologic study in 60 treated patients with a follow-up of 2 years.
Toxicity studies in rats with an impurity present in ICL-670 (Exjade).
Additional studies which although are not required, are recommended or requested.
Evaluation of safety and efficacy in 1,500 transfusional iron loading patients, outcomes. Exploration of the relationship between liver iron concentration, cardiac iron, serum ferritin and clinical endpoints.
Combination therapy of ICL-670 (Exjade) with deferoxamine in patients who are not responding or cannot tolerate ICL-670 (Exjade) alone.

pared and tested in preliminary clinical trials. A deferoxamine hydroxyethyl starch polymer and another starch deferoxamine polymer referred to as 40SD02 were both shown to increase iron excretion in healthy volunteers and iron-loaded thalassemia patients, respectively (70, 71). Both starch deferoxamine polymers were well tolerated and further long-term efficacy and toxicity studies are planned (70-72).

Conclusions

The current established therapy for thalassemia and other transfusional iron-loading conditions is based on the use of deferoxamine, deferiprone or their combination. The combination therapy recommended by the ICOC committee involving the administration of deferiprone during the day at 80-110 mg/kg/day and s.c. or i.v. deferoxamine at least 3 times/week at 40-60 mg/kg during the night appears to be universally effective for the treatment of transfused iron-loaded patients.

Several experimental iron-chelating drugs, including deferasirox, deferitrin, L1NAll and starch deferoxamine polymers, are undergoing clinical evaluation. None of these new chelators appears to be universally effective and nontoxic for all patients and it is likely that future treatments will involve combinations of chelators. The most advanced experimental chelating drug is deferasirox, the worldwide registration of which is expected shortly. Deferasirox appears to be effective in reducing liver iron but not cardiac iron levels. It is also ineffective in producing negative iron balance in most iron-loaded thalassemia patients.

Combination therapies using deferiprone, deferoxamine and new iron-chelating drugs are expected to increase iron excretion and reduce toxicity compared to monotherapy. Targeting iron removal from the heart will be a priority for future therapies and combinations with deferiprone will facilitate this process due to its cardiospecific iron-removing effect.

The upsurge in the development of new iron chelators has been prompted by the expanding and lucrative world market for iron-chelating drugs, which is currently estimated at USD 1 billion sales per year, and also by the expiration of the patents on deferoxamine and deferiprone. The high cost of the new chelating drugs may not facilitate the availability of new treatments to the vast majority of thalassemia patients who live in developing countries. However, effective therapy can easily be achieved by using deferiprone and deferoxamine combinations, especially when this can become available at low cost.

The prospect of using deferiprone, deferoxamine and new chelating drugs as monotherapies or in combination therapies in the treatment of other diseases is also likely to increase in the near future.

Notes added to proofs

ICL-670 (Exjade) was conditionally approved for use in the U.S. in November 2005, by the U.S. FDA under the provisions of accelerated approval regulations. It is specified that further adequate and well-controlled studies are needed to verify and describe clinical benefit. Details of some of the studies required are given in Table II.

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