Study of oral chelators of Deferiprone, Deferasirox and Deferoxamine and the need for alternative chelators in chelation therapy for transfusional iron overload in thalassemia major

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Abstract— **This article puts forward a comparative study of the three most common and widely used oral chelators of Deferiprone ,Deferasirox and Deferoxamine in the chelation therapy for transfusional iron overload in thalassemia .Thalassemia is a form of inherited autosomal recessive blood disorder characterized by abnormal form of haemoglobin.It is caused by variant or missing genes that affect how the body makes haemoglobin.People with thalassemia make less haemoglobin and have fewer circulating red blood cells (RBC) than normal.Complications caused by thalassemia includes iron overload,bone deformities and cardio-vascular diseases.In thalassemia major,blood transfusions can often lead to iron overload requiring chelation therapy. There is a need to develop certain drug oral chelators with high iron-binding potency and selectivity .The availability of such drug should be in abundance and with reasonable cost and should have minimum long term side effect .By knowing the 3D structure of the target molecule,we can design drugs that are capable of binding to receptor site of target protein with great affinity and specificity.We can evaluate binding affinity by docking and then modify the drug for desired property. Then biological evaluation can be done to evaluate the complex 3 D structure.**

Index Terms— **iron overload, Deferoxamine, Deferiprone, Deferasirox, oral iron chelator.**

I. INTRODUCTION

Chronic iron overload represents a serious complication of potentially lifesaving blood transfusions. Excess iron deposits in various tissues of the body, particularly the liver, heart, and endocrine organs.Once the body's storage capacity is exceeded, free iron catalyzes the formation of highly reactive hydroxyl radicals, which leads to membrane damage and denaturation of proteins. This process leads to tissue damage and ultimately to significant morbidity and mortality.

Indeed, organ failure due to chronic iron overload represents the major cause of death in patients with _-thalassemia major who receive blood transfusions regularly without appropriate chelation therapy. Within 1 to 2 years of initiation of regular blood transfusions, evidence of iron overload is manifest as elevated liver iron concentration (LIC) values and elevated serum ferritin levels. An increased risk of iron-induced cardiac disease is observed in thalassemia patients with LIC values above 15 mg Fe/g dry weight (dw), and in patients with serum ferritin values above 2500 g/L. Patients with a number of other congenital and acquired anemias who may receive frequent blood transfusions are also susceptible to the adverse effects of iron loading.

Unfortunately, due to the challenges of administering deferoxamine by slow subcutaneous or intravenous infusion over 8 to 12 hours, 5 to 7 nights per week, compliance with prescribed therapy is often poor, resulting in limited efficacy.In some countries, marketing authorization has been granted to theoral iron chelator deferiprone (Ferriprox;Apotex Toronto, ON, Canada),which is formulated as solid tablets and administered 3 times a day.

Prospective clinical data documenting the efficacy of deferiprone are limited. In addition, its therapeutic window is narrow, and its safety risks include drug-related agranulocytosis and arthropathy. Deferasirox (ICL670, Exjade; Novartis) is a member of a new class of tridentate iron chelators, the N-substituted bis-hydroxyphenyl-triazoles. It is orally bioavailable and its terminal eliminationhalf-life (t1/2) is between 8 and 16 hours, allowing for once-daily administration. Metabolism and elimination of deferasirox and the iron chelate (Fe-[deferasirox]2) is primarily by glucuronidation followed by hepatobiliary excretion into the feces. No significant drug-drug interactions have been identified to date. Preclinical studies demonstrated the ability of deferasirox to enter and remove iron from cells.

Previous studies in adult patients with thalassemia major revealed that treatment with deferasirox could potentially remove sufficient iron from the body to exceed that administered as part of a chronic transfusion regimen. This multinational phase 3 randomized trial comparing deferasirox to deferoxamine over 1 year was initiated in pediatric and adult patients with thalassemia receiving regular blood transfusions in order to further evaluate its efficacy in body iron reduction.Thalassemia was selected as the model disease for demonstration of efficacy across the range of patients at risk of iron overload.

II. DEFEROXAMINE

Deferoxamine (DFO; Desferal and generic) has been the standard iron chelator since the 1970s. DFO is both safe and effective for transfusional hemosiderosis. A hexadentate chelator, it binds iron tightly, and the iron-DFO complex is excreted in both urine and stool. DFO is administered as long parenteral infusions because the plasma half-life is short

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(minutes) and it is not active orally. Thus, it is given as an overnight subcutaneous infusion 5 to 7 nights/wk.

The DFO-iron chelate is charged and does not readily enter and leave cells. Parenteral administration and the daily nuisance of an infusion pump hinder optimal compliance. Nevertheless, in the DFO era, over the past generation, dramatic strides in survival of thalassemia patients have occurred.

III. DEFERIPRONE

Deferiprone (Ferriprox and others) is an orally active hydroxypyridineone first used in humans in 1987. Deferiprone is a bidentatechelator (3 molecules surround one iron ion). An advantage of thiscompound is that the iron(III) chelate of deferiprone carries no net charge and therefore can penetrate membranes easily, allowing removal of potentially toxic iron from tissues. Many *Blood* readers are aware of a controversy over the safety of deferiprone that arose in the late 1990s because of an observation of hepatic fibrosis during a clinical trial. However, in subsequent studies this problem has not been a significant toxicity issue for deferiprone. The history of deferiprone and this safety debate were well summarized in a 2003 *Blood* "Perspective." Deferiprone often causes gastrointestinal symptoms. Idiosyncratic side effects that are potentially severe include erosive arthritis (common in patients in South Asian countries, from 5% to 20%) and neutropenia (up to 5% of patients), including severe agranulocytosis (up to 0.5% of patients);close monitoring is required. Typical dosage for deferiprone is 75 mg/kg/d in 3 divided doses, up to 100 mg/kg daily.

IV. DEFERASIROX

Deferasirox (ICL670, Exjade) belongs to a new class of oral Tridentate chelator, N-substituted bis-hydroxyphenyltriazoles. Deferasirox,the result of a concerted discovery program, underwent extensive safety testing and clinical trials including preclinical studies, initial phase 1 and iron balance studies, phase 2 efficacy studies in adult and pediatric thalassemia patients, patients with a variety of anemias or unable/noncompliant with DFO, and the phase 3 clinical trial discussed here.With a plasma half-life of 8 to 16 hours, once-daily dosing permits circulating drug at all times to scavenge non–transferrin-bound "labile plasma iron," the chemical species responsible for tissue damage in iron-overloaded subjects, by means of toxic oxygen intermediaries. Deferasiroxiron complexes are excreted in the stool.

The 3 compounds are compared in Table below to properties of an ideal chelator. One "theoretical" advantage with real clinical import is access of chelators to intracellular iron, particularly in cardiac myocytes. In cultured heart muscle, deferasirox and deferiprone have rapid access to intracellular iron pools, whereas DFO does not. Nevertheless, high-dose continuous DFO, administered via central catheter, can dramatically reverse cardiac toxicity of iron overload. High-dose continuous DFO has been the "standard" initial therapy for cardiac iron overload.

Characteristic	DFO	DFP	DFX
Route of administration	Subcutaneous intravenous	Oral (tablets or solution)	Oral (dispersible tablet)
Usual dose	20–60 mg/kg/day over 8–24 hours	75–100 mg/kg/day in three divided doses	20–40 mg/kg/day
Stoichiometry	Hexadentate (1:1)	Bidentate (3:1)	Tridentate (2:1)
Excretion	Urinary Fecal	Mainly urinary	Fecal
Adverse effects	Auditory Ophthalmologic (retinal) Reactions at site of infusion Delay in bone growth *Yersinia* infection	Gastrointestinal Neutropenia/agranulocytosis Arthralgia Increase in liver enzymes	Gastrointestinal disturbances Gastrointestinal bleeding Increase in serum creatinine Rash Increase in liver enzymes Liver failure Renal insufficiency
Advantages	Long-standing experience	Most robust evidence on cardiac siderosis improvement	Once-daily dosing, oral
Disadvantages	Lack of compliance, parenteral	Frequent monitoring of CBC (weekly)	High cost
Licensed use in transfusion-dependent anemias	Treatment of chronic iron overload resulting from transfusion-dependent anemia	In Europe, North America, and Asia: treatment of iron overload in TM where DFO is contraindicated or inadequate	US: treatment of transfusional iron overload in patients 2 years or older Europe: treatment of transfusional iron overload in TDT patients, 6 years and older, and when DFO is contraindicated and inadequate, for patients 2–5 years old

V. EFFICACY OF A NEW ORAL IRON CHELATOR

Phase 3 trial results for deferasirox in a randomized controlled comparison trial with DFO are reported by Cappellini and colleagues. The trial involved nearly 600 patients (half were 16 years of age or younger) with transfusion-dependent thalassemia. The study was designed as a noninferiority trial, measuring hepatic iron by biopsy at baseline and after one year of therapy. Success was defined as either maintenance or improvement in HIC (depending on the baseline levels). Based on the study results, the United States Food and Drug Administration (FDA) approved the drug for transfusional iron overload for patients older than 2 years of age in November 2005. The drug is still under regulatory review in Europe.

This report deserves careful scrutiny from hematologists who care for patients with thalassemia and other disorders of transfusional iron overload. The dose choices for DFO and for deferasirox were based solely on baseline HIC at study entry. The decision to use this baseline value and the choice of what are now known to be relatively low deferasirox doses caused the study to fail to meet its overall primary end point (ie, at low doses of deferasirox, 5-10 mg/kg/d, increased HIC was observed). However, at doses of 20 to 30 mg/kg/d, the doses for HIC greater than 7 mg/g dry weight, noninferiority of deferasirox compared with DFO was established, with 60% versus 59% achieving a successful outcome, respectively. Assessed by ferritin concentration, 20 mg/kg/d deferasirox was sufficient to maintain mean ferritin levels over 52 weeks, whereas 30 mg/kg yielded a reduction in ferritin level. In retrospect, several design decisions contributed to the mixed outcome of "failure" at low doses and success at higher doses. For example, results from an earlier phase 2 trial of deferasirox in children, which also used low doses that proved ineffective, were not available in time to guide the phase 3 trial. As well, additional factors proved important in deferasirox efficacy. For example, transfused iron burden was shown to be a strong predictor of the iron response at a year. Likelihood of failing to achieve iron balance was much higher for patients receiving more than 0.5 mg/kg/d iron. Adverse drug reactions in deferasirox trials have included modest rise in creatinine level, rarely clinically significant.

Increased transaminases were observed occasionally. Common side effects of deferasirox include transient gastrointestinal symptoms in 15% and rash in 11%.

VI. COST COMPARISON OF DFO AND DEFERASIROX

Perfect and unbiased cost comparisons among commercial versionsof all 3 drugs are not yet possible for any single country, andnational price differences abound. Although a rough first-orderapproximation of price ranking might be deferiprone deferoxamine, deferasirox, this may not be true in every country . Nondrug obligatory costs are important as well: deferiprone therapy requires weekly complete blood count (CBC)/differential count; DFO requires ancillary supplies for infusion.

Deferasirox will cost more than twice as much as DFO in the United States. At least until deferasirox, chelators heretofore have not been the major cost of caring for American thalassemia patients; this dubious honor goes to the transfusions themselves. But the cost of deferasirox will be a significant new burden even in developed nations with strong health insurance programs, and it will be prohibitive in the developing world, without substantial discounts. An initial attemptat cost-effectiveness analysis was presented in abstract form at the American Society of Hematology 47th Annual Meeting in 2005, wherein the extra cost of the medication was weighed (favorably) against the cost of illness and death from noncompliance and iron
overload for DFO. This analysis was sponsored by the manufacturer.

VII. ADDITIONAL RECENT STUDIES OF DEFERASIROX

More than 20 deferasirox abstracts were presented at the 2005 American Society of Hematology Annual Meeting. These included clear evidence from both phase 2 and phase 3 clinical trials that transfusional iron loading (expressed as mg/kg/d of transfused iron) had a dramatic effect on the ability of deferasirox doses to maintain or reduce hepatic iron and presentation of the randomized trial of deferasirox versus DFO in sickle cell disease.

Porter et al demonstrated improved cardiac T2* with deferasirox in patients from their site in the phase 2 and 3 trials. Molar efficiency of DFO and deferasirox was compared by examining net iron balance as a function of input transfusional iron and chelator dose. These results have important implications to consider along with the phase 3 trial1: chelator efficiency and clinical effectiveness in vivo are not a function of chelate stoichiometry alone. Iron removal also depends on achievable plasma concentration, host factors, degree of loading, and rate of accessibility of stored iron to chelator.

VIII. CONCLUSION

For nearly 30 years, patients with transfusionaliron overload have depended onnightly deferoxamine infusions for ironchelation. Despite dramatic gains in lifeexpectancy in the deferoxamine era forpatients with transfusion-dependent anemias, the leading cause of death for young
adults with thalassemia major and related disorders has been cardiac disease from myocardial iron deposition. Strategies to reduce cardiac disease by improving chelationregimens have been of the highest priority. These strategies have included development of novel oral iron chelators to improve compliance, improved assessment of cardiac iron status, and careful epidemiologic assessment of European outcomes with deferiprone, an oral alternative chelator available for about a decade. Each of these strategies is now bearing fruit. The novel oral chelator deferasirox was recently approved by the Food and Drug Administration (FDA); a randomized clinical trial demonstrates that deferasirox at 20 to 30 mg/kg/d can maintain or improve hepatic iron in thalassemia as well as deferoxamine.Arandomized trial based on cardiac T2* magnetic resonance imaging (MRI) suggests that deferiprone can unload myocardial iron faster than deferoxamine. Retrospective epidemiologic data suggest dramatic reductions in cardiac events and mortality in Italian subjects exposed to deferiprone compared with deferoxamine. These developments herald a new era for iron chelation, but many

unanswered questions remain. Additional carefully designed studies are required to answer pressing questions about many drug combinations and treatment scenarios. Examples include both small-scale trials (eg, pilot pharmacodynamic studies of the 3 drugs in various combinations) and large-scale efforts (eg, initiation of a randomized,prospective phase 3 trial comparing deferasirox and deferaprone to assess relative safety, efficacy, and cardioprotection).

Life is short and science is long, opportunity is elusive, experiment is dangerous, judgement is difficult.

IX. HIPPOCRATES

Patients with thalassemia major and other transfusiondependent disorders who are able to successfully control iron overload at a safe level with deferoxamine should be encouraged to continue with this approach to chelation therapy. Treatment with deferiprone should be carefully considered for patients unable to use deferoxamine or for patients with an unsatisfactory response todeferoxamine as judged by liver iron and serum ferritin measurements or evidence of cardiac iron overload or iron-induced cardiac dysfunction. At a dose of deferiprone of 75 mg/kg per day, iron stores may decrease in some patients, remain stable in others, and increase in some others. Thus, careful monitoring of iron stores, preferably by measurement of tissue iron and of cardiac function, is important during treatment with deferiprone, as it is with deferoxamine. Enhanced iron excretion can be obtained at higher doses of deferiprone or by combining deferiprone and deferoxamine therapy.

Early studies of combined therapy are particularly encouraging, but these approaches have not undergone rigorous long-term testing for complications. Although we have focused on the use of deferiprone for thalassemia major, deferiprone may also have an important role in the treatment of patients with thalassemia intermedia and of patients with other anemias who accumulate iron at lower rates than do those with thalassemia major. As with any drug recently introduced to clinical practice, further studies of the risks and benefits associated with deferiprone therapy should take place, and   all patients receiving the drug should be closely monitored.

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