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Progress in the management of iron overload in erytrocyte disorders

A B S T R A C T

Although blood transfusions are essential for patients with hemoglobinopathies (ie Thalassemia, Sickle Cell Disease) or with rare anemias (ie Fanconi, Blackfan Diamond, PK deficiency), chronic transfusions inevitably lead to iron overload as humans cannot actively remove excess iron. The cumulative effects of iron overload lead to significant morbidity and mortality, if untreated. Desferrioxamine (DFO) is the reference-standard iron chelator whose safety and efficacy profile has been established through many years of clinical use. DFO side effects are accettable and manageable however the prolonged subcutaneous infusion regimen of 5-7 days per week is very demanding and results in poor adherence to therapy. Deferiprone (Ferriprox, L1) is a bidentate molecule, orally administrable three-times/day, licensed in Europe and in other regions but in the USA and Canada, for the treatment of iron overload in patients for whom DFO therapy is contraindicated or inadequate. Preliminary evidences suggest that deferiprone may be more effective than DFO in chelating cardiac iron. The side effects include gastrointestinal symptoms, liver dysfunction, joint pain, neutropenia and agranulocytosis. A weekly assessment of white blood cell counts is recommended because of the risk of agranulocytosis.
Deferasirox is a new, convenient, once-daily oral iron chelator that has demonstrated in various clinical trials good efficacy and acceptable safety profile in adult and pediatric patients affected by transfusion-dependent thalassemia major and by different chronic anemias (SCD, BDA, MDS). The long half-life of deferasirox (16-18 hours) provides sustained 24 hr iron chelation coverage. The efficacy and safety profile have been evaluated in more than 3000 patients in clinical trials. Patient satisfaction with deferasirox was superior than with DFO therapy.

Introduction

It is well known that red blood cell transfusions are a vital, life-saving treatment for many patients with chronic anemias including beta-thalassemia, Sickle Cell Disease (SCD), Fanconi's anemia, Blackfan Diamond, PK deficiency. Since every unit of transfused blood contains 200-250 mg of iron and the human body has no mechanism to actively excrete excess iron, cumulative iron overload is an inevitable consequence of chronic transfusion therapy.[1] The rates of transfusional iron loading have been extensively evaluated in patients with thalassemia major (TM) where they vary widely with an average

of 0.36 mg/Kg/day.[2,3] Among patients with SCD the transfusional requirements vary greatly; some HbSS patients receive only sporadic transfusions for intermittent complications, while others receive regular transfusions for prevention of stroke.[4]

The primary aim of iron chelation therapy is to bind to and to remove iron from the body at a rate that is either equal to the rate of transfusional iron input (maintenance therapy) or greater than iron input (reduction therapy). It has been established that iron chelation therapy reduces the risk of developing co-morbidities and improve patients survival during more than 40 years of clinical experience with the current reference standard chelator deferoxamine (DFO).[5] The second aim of chelation therapy is to provide constant, 24-hour protection from the harmful effects of toxic iron (ie NTBI), since gaps in chelation therapy result in iron reloading and further tissue damage.[6]

At present three iron chelators are currently available: desferrioxamine (DFO), deferiprone (L1), and deferasirox (ICL670) with distinct efficacy, safety and tolerability profile (Table 1).

Table 1. Comparison of the basic properties of the three chelators available in clinical use.

Property	*Chelators*			
	Ideal	*DFO*	*DFP*	*DFX*
Route	Oral	SC, IV	Oral	Oral
Molar Fe chelating eff.	High	1 : 1	3 : 1	2 : 1
Usual dose mg/kd/d	-	20-50	75-100	20-30
Half life	Long	20-30 min	3-4 hrs	12-16 hrs
Excretion	easy	Urine/FecalUrine	Fecal	
Full day LPI coverage	Yes	No	No	Yes
Penetration to tissue	+++	+	++to +++	++ to +++
Lowering liver Fe	+++	+++	+	+++
Lowering heart Fe	+++	++ (high doses)	++ to +++	++ to +++
Compliance	+++	+ to ++	++ to +++	++ to +++

DFO: Deferoxamine, DFP: Deferiprone, DFX: Deferasirox

Desferrioxamine

Desferrioxamine has been in clinical use since the 1970s and widely used as subcutaneous infusion since about 1980. Due to its molecular size, it is poorly absorbed from the gut. Desferrioxamine has a short plasma half-life (initial half-life 0.3h), being eliminated rapidly in urine and bile. The process of iron chelation ceases soon after an infusion of desferrioxamine is completed.[7] When desferrioxamine use was introduced in clinical practice, the solution was administered intramuscularly, however the clinical experience showed that intramuscular injections were less effective than slow subcutaneous infusions by infusion pumps due to the relatively rapid plasma clearance.[8] Continuous intravenous infusions using slow infusion by Portacath were recommended in patients with severe cardiomyopathy related to iron overload, in patients with local adverse drug reactions or in patients non-compliant to subcutaneous infusion. Desferrioxamine had a well established impact on survival and on cardiac and other complications of iron overload.[9,10] Since the introduction of desferrioxamine, the incidence of iron induced heart disease and deaths in thalassemia have fallen progressively in cohorts of patients – with a key factor being the age of starting treatment. Symptomatic heart disease can be reversed by high dose intravenous treatment.[11] However, recent data show that a significant portion of patients on long term s.c. DFO with good compliance and low serum ferritin levels has evidence of cardiac iron loading. Interestingly, the introduction of MRI T2* technique for measuring iron loaded in the heart showed a poor relationship between cardiac iron and liver iron in long-term treatment with DFO, measured by MRI, liver biopsy, SQUID or serum ferritin.[12] Because of the drug development at the early seventhies, most of the results on desferrioxamine use were based on observational

reports. The results of a formal prospective study on the dose required to stabilise or decrease serum ferritin in large populations have only recently become available. The study – a prospective evaluation of changes in ferritin levels and LIC as a function of dose in 290 thalassaemia major patients – demonstrated that a mean daily dose of 42 mg/kg resulted in a small decrease in serum ferritin of 364 µg/L at one year, whereas a mean daily dose of 51 mg/kg resulted in an average ferritin decrease of approximately 1,000 µg/L over one year.[5] Therefore, if the serum ferritin is >2,500 µg/L, a mean daily dose of at least 50 mg/kg/day is recommended, except in children because of negative effect on growth.

Although desferrioxamine during the last 30 years has changed the outcome of morbidity and mortality for thalassemia, the poor patients adherence to the effective standard treatment and the non availability in several countries because of costs remain two major concerns that significantly limited the beneficial effects of iron chelation.

Desferrioxamine side effects

Local skin reactions, such as itching, erythema, and mild to moderate discomfort are common. Local reactions may in some cases be associated with systemic reactions, including fever,urticaria, headaches, myalgias or arthralgias. Skeletal changes in children have been reported in cases of excessive dosage of desferrioxamine Most of these effects may be prevented using DFO doses lower than 50 mg/kg/day and modulating the dosage according to the iron load level. Ophthalmological and audiological tests should be carried out before starting treatment with desferrioxamine as well as yearly during treatment. Infection with Yersinia enterocolitica is an important risk associated with desferrioxamine treatment. (TIF guidelines 2007 www.thalassaemia.org.cy).

Deferiprone

Deferiprone (Apotex, Toronto, ON, Canada) also known as L1, CP20, Ferriprox and Kelfer was synthesized and tested as iron chelator at the University of Essex in the early 1980s.[13] Deferiprone is a bidentate molecule that forms 1:3 iron-chelator complexes. It is rapidly absorbed and the mean half-life was reported 160 and 91 minutes respectively in two different studies deferiprone has a low molecular weight (139) that facilitates penetration into cells. At present deferiprone is licensed and currently available in the European Union and in a number of countries outside the USA and Canada for the second-line treatment of iron overload in patients with thalassemia major for whom DFO therapy is contraindicated or inadequate (EMEA). The effect of deferiprone treatment on liver iron concentration (LIC) was variable and not comparable among studies because of different length of treatment and different dosages. Based several results it seems that deferiprone at standard dose of 75 mg/Kg/day orally administered (3 times/day) is similar to DFO at removing iron from the liver although great individual variations have been observed.[14] A systematic review based on Cochrane database (July 2007) selecting randomized controlled trials comparing deferiprone with DFO or comparing two schedules of deferiprone in patients with transfusion dependent thalassemia has been recently published. There was no consistent effect on reduction of iron overload between all treatment comparisons with the exception of urinary iron excretion that was in favour of deferiprone in one trial and of DFO in 3 trials.[15] Deferiprone by virtue of his membrane crossing ability has been shown to shuttle tissue iron into circulation and studies in iron-loaded rat heart cells and in gerbils had shown his ability to remove iron from myocardial cells.[16] Recently several evidences, although

some are based on retrospective analyses, have been accumulated suggesting that deferiprone is superior to DFO at removing cardiac iron. Borgna-Pignatti[17] using the data available from 7-center Italian database, compared development of cardiac disease and survival in patients chelated only with DFO and in patients who had their therapy switched to deferiprone during the period of observation from January 31,1995 to December 31, 2003. Fifty-two cardiac events, including 10 cardiac deaths, occurred during therapy with DFO, whereas no cardiac events were recorded during Deferiprone therapy or within at least 18 months after the end of it. Pennel *et al.*12 showed an improvement of myocardial T2* greater for deferiprone (>75 mg/kg) than DFO (27% *vs.* 13%, p=0.023) whereas the changes in liver iron concentrations and serum ferritin levels were not significantly different between the 2 groups. Several other studies strongly suggest that deferiprone, probably because of its lower molecular weight and greater intracellular penetration is more effective at removing iron from the hearth than DFO,[18] however some cardiac deaths have been reported also in patients on deferiprone[19] suggesting that deferiprone alone is not sufficient to rescue severe iron overload and particularly in a short period of time. The major direct benefit of iron chelation therapy to the heart is the continuous removal of non-transferrin-bound iron (NTBI) from plasma. Iron chelation must therefore provide continuous 24-hour cover to maximize chelation efficiency. NTBI re-form within minutes of removal of the chelating agent from plasma. Deferiprone can decrease plasma levels of some NTBI species but the duration of protection is limited to 2-3 hours after drug ingestion.[20] Based on this observation it was considered that combination of deferiprone and DFO could be a possibility to optimize body iron removal.

Deferiprone and deferoxamine combination therapy

Wonke *et al*. in 199821 reported on 5 TM patients safely treated over several months with deferiprone and DFO given on the same day. Since than data from several cohorts of patients treated with deferiprone and DFO in combination have been reported. Unfortunately the wide range of dosing and scheduling makes the comparison of the results difficult, nevertheless quite homogeneous results showing a fall of serum ferritin levels, were reported compared to monotherapy.[22,23] Recently, a randomized placebo controlled double blind trial showed that combined treatment is superior to DFO alone at removing myocardial iron in TM patients and improving cardiac and endothelial function.[24] Recently it has been shown that deferiprone given at daily dose of 75 mg/kg in combination with DFO (40-50 mg/kg) twice weekly is efficacious and safe providing superior chelation activity to that of deferiprone alone and likely has an efficacy profile comparable to that of standard DFO.[25] A single uncontrolled study suggests that combination therapy may reverse endocrinological complications as glucose intolerance in thalassemia patients, however the data are too preliminary to lead conclusions.[26]

Deferiprone side effects

Gastrointestinal symptoms (GI) including nausea, abdominal pain and vomiting are the most common and in general occur in the first year of treatment. Incidence of GI symptoms vary from 24-33%. Transient or fluctuating rise of serum hepatic transaminase levels has been reported either in hepatitis C positive or negative patients.[27] Arthropathy and/or arthralgia are quite common side effects particularly frequent in patients from India.[28] The most serious side effects reported during treatment with Deferiprone are neutropenia and agranu-

locytosis. It is still difficult to properly estimate the incidence of agranulocytosis in patients on Deferiprone since the monitoring is not strictly respected. The EMEA recommends a weekly monitoring of white cell count during Deferiprone treatment with discontinuation of drug with a neutrophil count $<1.5\times10^9$/L. For patients who experienced an episode of agranulocytosis the drug should not be reintroduced. The prevalence of agranulocytosis and neutropenia in patients on combined treatment with DFO and deferiprone, seems to raise significantly (2% and 5,6% respectively) (*Kattamis A, personal communication*). On the overall 5-10% of patients discontinued the drug because of side effects. A high dropout rate of 30-40% after 4 years of treatment in a single study has been reported.[27] The efficacy and safety of Deferiprone in iron-loaded patients with sickle cell anemia or other rare anemias are not fully documented and long-term prospective trials are needed before suggesting Deferiprone use in such condition.

Deferasirox

Deferasirox (ICL670, Exjade®) is a tridentate-bis-hydroxypheny-triazole chelator with a molecular weight of 373.36 Two molecules of Deferasirox are required to bind one Fe^{3+}; forming a stable 1:2 iron-chelator complex. Deferasirox has a long half-life (8-16 hours) which means that it can be taken once a day.[29,30] It is formulated in tablets that should be completely dissolved by stirring in water, orange juice or apple juice. As demonstrated in various animal models, deferasirox is rapidly absorbed, can efficiently and selectively mobilize iron from various tissues such as hepatocytes and cardiomyocytes, and can promote iron excretion. The deferasirox-iron complex is excreted in the feces and not redistributed.[29,30] Deferasirox is currently approved in many countries, including the USA, Switzerland, and Europe, for the treatment of chronic transfusional iron overload in adult and pediatric patients (Exjade PI 2005). Deferasirox plasma levels were shown to be maintained within the therapeutic range over a 24-hour period (20 mg/kg/day: peak levels ~60-100 µmol/L, trough levels ~15-20 µmol/L), providing constant gap-free chelation coverage with a single daily dose (study 101).[31] The results in pediatric patients showed no differences in maximum concentration and half-life between children (aged <12 years) and adolescents (aged ≥12 years), although exposure to deferasirox was approximately 20-30% lower than that previously observed in adult β-thalassemia patients.[32] The effective dose was established between 20-30 mg/kg/day. Pivotal data have been recently published from a large-scale, randomized Phase III trial comparing deferasirox (n=296) with subcutaneous DFO (n=290) in regularly transfused adult and pediatric patients with transfusion-dependent β-thalassemia (Study 107).[2] Dose was assigned according to baseline LIC. The results showed that iron balance was achieved at the recommended deferasirox starting dose of 20 mg/kg/day, and a significant reduction in iron burden was observed at 30 mg/kg/day.[2] Overall, changes in LIC, serum ferritin and body iron balance were consistent during the study and correlated well with one another. More recently a randomized controlled trial demonstrated that deferasirox is equivalent to DFO in sickle cell anemia.[33] Pooled data from across the deferasirox clinical trial program have demonstrated that the response to deferasirox is not only dependent on dose, but also on the rate of transfusional iron intake while on study[3] Although the impact of transfusion rate was underestimated in these studies, it did enable a comparison of various transfusion rates at each dose leading to some general guidance for deferasirox dos-

ing: 10 mg/kg/day are advisable for maintaining iron balance in patients with low transfusional requirements (<2 units of blood/month); 20 mg/kg/day for maintaining or reducing iron balance in patients with low and intermediate requirements (2-4 units of blood/month) and 30 mg/kg/day for decreasing iron balance in most patients, irrespective of transfusional requirements.[34] A number of regularly transfused patients with different chronic anemias have also been studied, including SCD and Diamond-Blackfan anemia (DBA). Preliminary data from patients with DBA (Study 108), as well as SCD (Study 109), demonstrate significant, dose-dependent effects on LIC and serum ferritin over the 1-year treatment period, which were similar to results seen in thalassemia patients.[35] As discussed previously, deferasirox has a long half-life and significant plasma levels are present after 24-hour period. This means that with deferasirox it is affordable and relatively easy to achieve a continuous and long lasting iron chelation coverage that may potentially prevent iron toxicity effects. Preliminary data in patients with β-thalassemia demonstrate that daily trough levels of deferasirox are sufficient to maintain suppression of LPI levels, suggesting that deferasirox is able to control LPI for 24 hours with a single dose After 4 weeks of treatment with deferasirox (20 mg/kg/day), peak LPI levels observed just before deferasirox dosing were significantly decreased compared with baseline and were close to normal levels.

Preliminary clinical data show that deferasirox is also effective for removing excess cardiac iron, as measured by an improvement in myocardial T2* over 1 year of treatment in most thalassemia patients Recent data presented at ASH 2007 (Cappellini ASH 2007) showed that over 3.5 years of treatment, Deferasirox continues to have clear dose-dependent efficacy. In patients who initially received deferasirox 5/10 mg/kg/day in the 1-year trials, serum ferritin levels steadily decreased below baseline once doses were increased to an appropriate level (~20 mg/kg/day) in the extension trials. Deferasirox has dose-dependent efficacy and, when dosed correctly, is effective for maintaining and reducing iron levels over a long-term treatment period (3.5 yrs). It is now clear that dose must be titrated for each patient according to the rate of iron intake from ongoing blood transfusions, current iron burden, safety markers and target serum ferritin levels for individual patients.[36]

Deferasirox side effects

Of 652 patients who received deferasirox in the core clinical trials (Studies 106, 107, 108, and 109), none experienced drug-related neutropenia or agranulocytosis, which were serious adverse events observed during treatment with other chelators.[2,32,33,35,36] Sporadic cases were observed, but most were considered by the investigators to be due to the underlying condition.The most frequent adverse events (AEs) reported during chronic treatment with deferasirox include transient mild-to-moderate gastrointestinal disturbances (~26% of patients) and transient mild-to-moderate skin rash (~7% of patients). These events rarely required drug discontinuation and many resolved spontaneously. Mild, non-progressive increases in serum creatinine (generally within upper limit of normal [ULN]) were observed in 34% of patients, requiring dose reduction in 10%, although these changes are not currently thought to be clinically relevant. No patients permanently discontinued therapy due to creatinine rises in the core, 1-year studies. Increases above the ULN were observed in 2% of patients with β-thalassemia major and 16% with other anemias, including geriatric patients whose baseline creatinine levels were close to the ULN. Extension studies are

ongoing to collect long-term data on these increases in serum creatinine. No conclusive mechanistic explanation is yet available for serum creatinine changes, but patients in trials with the increases were generally those with the greatest and rapid reduction in iron burden. Some patients (0.3%) experienced elevated alanine aminotransferase levels (>5x ULN). Deferasirox is also generally well tolerated in children as young as 2 years of age, with a safety profile similar to that observed in adults.[36] Over 3.5 years of follow-up there was no increase in frequency of drug-related adverse events or changes in markers of liver or renal function that differed significantly from the 1-year core trials.

In postmarketing use, a small number of acute renal failure have been reported [(Exjade (deferasirox) prescribing information. Novartis Pharmaceuticals Corporation 2007. Available at http://www.exjade.com)]. However in many of these patients confounding factors to explain renal failure were detected such as pre-existing renal dysfunction, advanced age, co-morbidities or concomitant medications. Although no cases of drug-related cytopenia were reported during clinical trials, postmarketing data showed some reports of neutropenia and thrombocytopenia in patients treated with deferasirox. Most of the patients had pre-existing hematological disorders that are frequently associated with bone marrow failure or it occurred in case of thalassemia or sickle patients where hypersplenism was pre-existing.

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