

## **Orally Active Chelators**

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Since Deferioxamine first became widely used as a chelator in transfusional iron overload there has been a need for a simpler and more efficacious form of chelation. This search has resulted in the discovery and clinical use of 2 orally active chelators and there are a number of chelators, which are still in clinical development. Despite oral chelation being widely used adherence remains a major issue and must be addressed on a regular basis to ensure that side effects are not hindering effective chelation.

### **Deferiprone (Ferriprox<sup>®</sup>, Kelfer<sup>®</sup>, L1)**

Deferiprone is of the hydroxypyridinone class of chelators and was first identified as a chelator by Kontoghiorghes in 1985 (Kontoghiorghes GJ and Evans RW 1985, Kontoghiorghes GJ, *et al* 1987). It is orally active and has been evaluated extensively in clinical trials.

It is licensed in Europe as second line therapy for patients unable to take deferioxamine and not currently licensed in the United States.

### ***Pharmacology***

Three molecules of deferiprone are required to bind one iron atom, and the efficiency of iron binding decreases with falling concentrations of iron or of chelator. The drug is rapidly metabolised and inactivated in the liver by glucuronidation of one of its iron binding sites. At currently used doses, about 5% of the drug binds iron before it is excreted or metabolised. Unlike deferioxamine, iron excretion is almost exclusively

in the urine. The effect of ascorbate on iron excretion with deferiprone is not clear but is potentially harmful and is not recommended.

### *Side effects*

#### Agranulocytosis:

This is the most serious adverse event and several studies have reported the incidence at <1% (Ceci, *et al* 2002, Cohen, *et al* 2000, Cohen, *et al* 2003, Kontoghiorghes, *et al* 2003) Milder forms of neutropenia (ANC 500 - 1500/mm<sup>3</sup>) occurred in <5% of patients. The incidence of Neutropenia is higher in patients below the age of 18 and those who have not been splenectomised. In these patients it is recommended that the ANC be monitored every week, or more frequently if there are signs of infection. In older patients who have been splenectomised the count should be monitored weekly for the first 6 to 8 weeks and thereafter fortnightly. It is imperative that the patient is aware of the risks of neutropenia and attends hospital urgently if they have a sore throat or fever. Neutropenia and agranulocytosis resolve on discontinuation of treatment with deferiprone. If agranulocytosis occurs, treatment is the same as for other causes of agranulocytosis and include hospital admission if unwell with administration of Intravenous antibiotics as per local neutropenia sepsis guidelines and the use of growth factors in severe sepsis. Recovery of the neutrophil counts will occur between 1 to 4 weeks after discontinuation of Deferiprone (Ceci, *et al* 2002). Deferiprone should not be reintroduced for such patients.

#### Arthropathy:

An erosive large joint arthropathy has been described and reports vary from 4% to 25% of patients. Deferiprone should be stopped in those patients with symptoms and X rays of the affected joints taken. If there is evidence of erosive arthropathy then deferiprone should be stopped

on a permanent basis. If there is no evidence of arthropathy then deferiprone may be cautiously re introduced but should symptoms reoccur then permanently withheld.

Other side effects:

Serum ALT levels are often raised and will fluctuate. No progression to worsening has been seen on trend analysis in 2 large studies (Ceci, *et al* 2002, Cohen, *et al* 2003).

Gastrointestinal upset (nausea, vomiting and diarrhoea) occur frequently in the first year. Giving deferiprone with meals may help to reduce nausea. Weight gain has also been documented as a side effect and needs to be monitored, as the patient may need appropriate dosage adjustments. Zinc deficiency during deferiprone therapy has also been observed in some patients, especially those with diabetes. Deferiprone is teratogenic in animals and must never be given to patients attempting to conceive. It should be stopped 3 months prior to sperm collection or ovulation induction. Potentially fertile sexually active women and men taking deferiprone must use contraception.

***Monitoring treatment***

Careful monitoring of the patient's clinical condition and laboratory examination during therapy with deferiprone is essential. Weekly blood counts are highly recommended so that a falling white cell count can be detected early and treatment stopped. Liver iron quantification before and during therapy is advisable as well as careful histological review in those patients who are hepatitis C virus RNA positive to look for progression of cirrhosis. In patients who have has an episode of neutropenia on Deferiprone agranulocytosis is more likely and Deferiprone should be used only with extreme caution and frequent monitoring.

## Deferasirox (Exjade, ICL 670)

Deferasirox is an N substituted bis-hydroxyphenyl-triazole which is a new class of synthetic tridentate chelators. It underwent extensive preclinical animal studies and was found to be a potent and selective oral iron chelator. It was well absorbed and tolerated in the phase 1 and 2 studies (Nisbet-Brown, *et al* 2003) and 20mg/kg doses have been found to be non-inferior to DFO with regards hepatic iron clearance and ferritin values (Cappellini, *et al* 2004, Cappellini, *et al* 2006, Piga, *et al* 2004).

Deferasirox is licensed for the treatment of transfusional iron overload in patients with beta thalassaemia major aged 6 years or older, or those greater than 2 years of age in whom deferioxamine is contraindicated or inadequate. It is also licensed for use in patients with other transfusion dependant anaemias where the transfusion requirement may be less frequent.

### *Pharmacology*

Two molecules of Deferasirox bind to one molecule of ferric iron. Deferasirox has a half-life of 11 to 19 hours. It has variable absorption with food and should be taken on an empty stomach generally 30 minute before food. Deferasirox is metabolised and inactivated by glucuronidation and a smaller amount by of hydroxylation. At recommended doses the efficiency of iron binding is approximately 12% at 20 mg/kg/day doses. Excretion of both free drug and iron bound forms is almost exclusively in the faeces.

### *Side effects*

During large phase 2 and 3 studies, side effects that were thought to be associated with the drug were skin rash (10%) transient nausea (20%), diarrhoea (20%) and abdominal pain and vomiting (15% each).

#### Management of skin rash:

These tend to appear within the first 3 weeks of therapy and are macular-papular in appearance. If the rash is of mild/moderate severity and relatively asymptomatic Deferasirox can be continued and the rash will resolve spontaneously over the next couple of days. If the rash is moderately severe then Deferasirox should be discontinued and re initiated at 50% dose reduction once the rash has resolved. The dose can be escalated slowly back to full treatment dose over several weeks provided the rash does not reoccur. If the rash is severe (distressing symptoms requiring systemic steroids for symptom relief) or if it reoccurs on reintroduction at 50% dose reduction, treatment should stop until complete resolution and re-introduction attempted at 25% of the initial dose. At this time systemic steroid cover should be used and the dose of Deferasirox increased at 25% increments at 4 weekly intervals provided that the rash does not reoccur

#### Management of rises in the serum creatinine:

Mild rises in the serum creatinine were observed in 30% of patients and these resolved on dose reduction.

- For patients aged 15 years or older:

If the creatinine increases by 33% or greater on at least 2 occasions more than 2 weeks apart, the dose should be reduced by 5 mg/kg if the

total dose is 20mg/kg/day or less, and by 10 mg/kg/day if greater than 20mg/kg/day.

- In children less than 15 years of age:

Changes that result in the creatinine rising above the age related upper limit of normal (ULN), and are more than 33% of the baseline value on more than 2 consecutive occasions greater than 2 weeks apart, will require a dose reduction similar to that outlined above. Increases in the serum creatinine that are above the ULN and less than 33% of the baseline do not require a reduction.

Serious adverse events have been rare and no cases have been reported of arthropathy or agranulocytosis. The long-term data on complications in young children, effect on growth and development, survival and the incidence of iron-associated complications will become clearer over the next 10 years or so. In addition although the animal toxicology studies have not found teratogenicity or genotoxicity Deferasirox should be stopped in patients who are attempting to conceive. Potentially fertile patients should use appropriate contraception.

#### *Monitoring treatment*

Monitoring should include monthly serum creatinine values or more frequently if indicated. All patients should have an annual ophthalmology assessment to look for treatment related cataracts and audiometry assessments.

#### **Approaches to treatment:**

There are a number of therapeutic options for patients with transfusional iron overload. The chelator with which there is the greatest experience and long-term safety data on is Deferioxamine.

Chelators currently licensed as first line treatment in iron overload are Deferioxamine and Deferasirox. Deferiprone is licensed as second line treatment in patients who are unable to adhere to Deferioxamine in Europe and is not currently licensed in the USA. The choice of chelator to use for patients should be an individualised one. Factors that need to be considered are:

1. Complications with previous chelators
2. Ability to adhere to the treatment regimen for both the patients and the carers in the case of children
3. Affordability and availability
4. Iron related organ damage
5. Patient/parent choice

#### **Treatment of children starting chelation for the first time:**

Currently first line chelation treatment in children with thalassaemia major below the age of 6 years remains Deferioxamine until there is greater long-term safety data available for the oral chelators in this age group. For children who are poorly compliant to Deferioxamine, every effort should be made to improve treatment through repeated counselling and exploration of alternative regimens of Deferioxamine administration. If these efforts fail, or if patients are unable to take Deferioxamine for other medical reasons, Deferasirox (Exjade, ICL670) may be considered as an alternative treatment in this age group.

#### **Chelation for children older than 6 and adults:**

This is dependant on choice and availability.

Many patients will choose to continue with Deferioxamine as they are familiar with this regime and are able to adhere to treatment plans. There are a cohort of patients who find Deferioxamine difficult to

adhere to and would like to transfer onto an oral chelator. Deferasirox is licensed as first line therapy in these patients but it is very important that patients and parents are aware that the long-term data is not available on Deferasirox and they will require regular attendance at hospital for monitoring.

Some patients may benefit from Deferiprone or combination therapy using Deferioxamine and Deferiprone and these patients will be discussed later. There is no evidence on the safety of combination therapy of Deferasirox with either Deferioxamine or Deferiprone and this should not be considered outside the context of clinical trials following validated safety monitoring procedures and ICP- GCP guidelines.

### Chelation regimens using oral chelators

#### **Deferiprone as a single agent:**

The daily dose of Deferiprone that has been evaluated most thoroughly is 75 mg/kg/day, given in three equally divided doses (Al-Refai FN, *et al* 1995, Ceci, *et al* 2002, Cohen, *et al* 2000, Victor Hoffbrand 2005). Most of these studies have assessed the safety of deferiprone and found this dose be effective in reducing the serum ferritin in some but not all patients. More recently randomised controls trials have compared Deferiprone at 75 mg/kg/day (Ceci, *et al* 2002) and 92 mg/kg/day (Pennell, *et al* 2006) to Deferioxamine ( 40 to 50 mg/kg) using liver iron concentration (LIC) as a marker of effectiveness and found it to be as effective as Deferioxamine at clearing hepatic iron burden. However there is great individual variation and some patients will be effectively chelated with Deferiprone monotherapy whilst others will not. In view of this variability in response it is recommended that if the serum ferritin is not falling with Deferiprone the dose should be

increased up to a maximum of 100mg/kg/day provided that the side effects are tolerable. Once the ferritin falls below 1000ng/ml then the hepatic iron burden should be re-assessed and a reduction in dose should occur with the aim being to maintain the ferritin at below 1000ng/ml and the hepatic iron burden less than 5 mg/g/dw.

### Monitoring treatment

Careful monitoring of the patient's clinical condition and laboratory examination during therapy with Deferiprone is essential, liver biopsies before and during therapy are advisable. It is important to not be complacent about high hepatic iron in patients on Deferiprone monotherapy as serious endocrinopathies are associated with the severity the hepatic iron burden. Patients must be encouraged to ensure that the hepatic iron is brought as low as possible in order to reduce the risk of diabetes and also hepatic cirrhosis. In those patients where the hepatic burden remains high then alternative chelation regimes must be considered either in the form of combination therapy with Deferioxamine or Deferasirox monotherapy.

It is also important to check in cases where the ferritin is not falling that Deferiprone is being taken correctly.

### **Chelation treatment using Deferioxamine and Deferiprone**

There are number of regimens that can be used. All by and large use Deferiprone as described above on 7 days a week. Deferioxamine can be added into the regime as described below:

1. Sequentially in order to provide 24 hour chelation cover as a 12 hour infusion overnight

2. Combination treatment using both agents simultaneously with deferioxamine as a 12-hour infusion during the day or as a 24-hour infusion on 2 to 7 days a week.
3. Variations of the sequential regimen with deferiprone used on some days and deferioxamine on other days but not on the same day.

There are some theoretical benefits from using both chelators together and there is evidence from iron balance studies that net negative iron balance is achieved using both agents together (Glickstein, *et al* 2006, Kattamis, *et al* 2003, Kattamis, *et al* 2006, Origa, *et al* 2005). In view of this combination therapy should be considered for patients with heavy iron burden and patients should be fully involved in the decision to use combination therapy.

#### Monitoring treatment

Patients receiving combination therapy will by and large have higher initial serum ferritin values and frequently evidence to support myocardial iron loading. Monitoring must take into account the side effects of both chelators. The ferritin values should be monitored regularly and the hepatic iron either using liver biopsy or MRI techniques. The cardiac function in patients with evidence of myocardial iron loading should be monitored using locally available methods. The dosage of Deferioxamine must be adjusted in keeping with the therapeutic index in order to avoid Deferioxamine toxicity and once the ferritin falls below 1000ng/ml then the hepatic iron should be reassessed and consideration given to single agent regimes.

#### **Deferasirox**

Phase 2 and 3 studies have shown that the 20mg/kg/day is as effective as 40 mg/kg/day of Deferioxamine (Cappellini, *et al* 2006, Piga, *et al*

2006). This should be the starting dose for patients on regular transfusion regimes that require greater than 7ml/kg/month of packed red cells. In those patients with a less frequent transfusion regime the starting dose should be 10-15 mg/kg/day. Ferritin levels and serum creatinine must be monitored as outlined above and doses adjusted appropriately if the serum ferritin rises. Increment in dose if required should be in the order of 5mg/kg/day and a decrease in the dose should occur as outlined above if the serum creatinine rises.

#### **Chelators and myocardial iron clearance:**

On a theoretical level if patients are appropriately chelated and the amount and duration of chelation administration is sufficient as originally described by Gabutti and Piga (Gabutti and Piga 1996) then patients will by and large remain well and free of cardiac complications. Myocardial iron loading often develops due to treatment being incorrectly taken in the erroneous belief that total dose is more important than the duration over which this dose is administered or simply poor adherence. The binding of toxic iron species by chelators is the most important effect of chelator agents (Gosriwatana, *et al* 1999, Pootrakul, *et al* 2004).

Several studies have shown that all iron chelators do remove intracellular iron (Glickstein, *et al* 2006, Roberts S and Bomford A 1988) and there is considerable evidence on the cardioprotective effect of Deferioxamine in terms of survival data and in use as salvage therapy in patients who have cardiac failure secondary to iron overload (Davis, *et al* 2004, Davis and Porter 2000). However until recently there was no clear evidence on the cardioprotective effect of oral chelators. This data is rapidly accumulating for Deferiprone and there is now evidence to support myocardial iron clearance by improvements observed in the end systolic volume, ejection fraction and other MRI

parameters such as Cardiac T2\* (Origa, *et al* 2005, Pennell, *et al* 2006, Wu, *et al* 2004) and also some epidemiological evidence to support a reduction in cardiac complications in patients using Deferiprone (Borgna-Pignatti, *et al* 2006). Deferiprone should be considered as part of a chelation regime in patients who have evidence of myocardial iron loading especially when adherence to Deferioxamine has been suboptimal. Although it is too early for any but very preliminary data to be available for Deferasirox there is some data in abstract form on improvements in myocardial T2\* (Porter, *et al* 2005). The role of oral chelators in treatment and prevention of cardiac iron overload will become clear in the next few years as greater long term data accumulates.

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