

Clinical Guidance

Guidelines for iron chelation in adults with a haemoglobinopathy or other inherited anaemia diagnosis

These comprehensive guidelines are intended for use as a reference for medical, nursing staff and all health care professionals

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INTRODUCTION

Iron accumulation is an inevitable consequence of chronic blood transfusions. Per unit transfused a patient receives approximately 250mg of iron which they are unable to excrete. In the absence of iron chelation therapy the iron accumulates in a variety of organs like the heart, liver and pancreas resulting in complications such as heart failure, diabetes, hypothyroidism, liver failure, as well as early death. Additionally patients, especially those with Thalassaemia, similar to haemochromatosis patients, have increased iron absorption from their gut in addition to the transfusion al iron load.

Before commencing chelation:

The decision to commence chelation should be made by (or in consultation with) a Consultant Haematologist experienced in the use of iron chelators. Chelation therapy is long term treatment and good patient compliance over a number of years is the only way to achieve treatment aims hence involvement of the patient early in decision making is key.

All patients:

- Should have a full discussion backed with written information on iron overload.
- Should be informed about the goal of iron chelation and understand its preventative nature.
- Should be fully informed about the choice of chelators available and the safety profile of each.
- Must understand how their treatments will be monitored.

Aim of Therapy

The goal of iron chelation therapy in these patients is to prevent the toxic effects of iron overload, it is long term therapy hence the choice of treatment needs to have a good side effect profile and be delivered by a route that will encourage compliance in each individual patient.

Therapy goals:

- Maintain iron balance and avoid accumulation of iron aiming for:
 - Average annual Ferritin <1000mg/L (+/-500),
 - Liver iron concentration (LIC) <5mg/g dry weight,
 - Cardiac T2* >20ms
- Prevent organ dysfunction
- Prolong survival
- Avoid chelator toxicity
- Maximise adherence to therapy

Indication for treatment

Homozygous sickle cell patients (occasionally Hb SC or S-Beta thalassaemia compound heterozygote) on regular top-up transfusion regimens.

Beta Thalassaemia major patients on lifelong transfusions (this includes Beta-E thalassaemia compound heterozygotes)

Beta thalassaemia intermedia patients.

Other patients on regular transfusion regimens e.g. Myelodysplasia, hereditary anaemias, etc

Assessment of Iron burden:

- Serum Ferritin > 1000mg/L (measured in steady state with normal inflammatory markers on 2 or more occasions > 6 months apart)
- R2 Liver MRI - liver Iron > 7mg/g/dw.
- Cardiac T2*MRI - < 20ms

Special Considerations:

Sickle cell patients

Drug choice: Deferasirox has been compared to Desferrioxamine in a phase III study of children and adults with sickle and appears to be safe and equally efficacious and there is very little data on use of Deferiprone in sickle cell disease, so Deferiprone monotherapy may only be considered in individual circumstances at the discretion of the Consultant Haematologist. The choice is between Desferrioxamine and Deferasirox. Deferasirox is usually offered as initial therapy because of ease of delivery but the current state of knowledge of efficacy and toxicity of both agents should be discussed with the patient to allow a decision to be taken collaboratively by patient and clinician.

Renal impairment is relatively common in adults with sickle cell, and the serum creatinine is not a sensitive marker. There have been cases of renal failure in patients with sickle cell disease on Deferasirox. This is expected to be a particular risk during a severe vaso-occlusive crisis or other sickle related complications. Monitoring of renal function, avoidance of other nephrotoxic drugs and maintenance of adequate hydration is especially important for these patients

Monitoring: Ferritin levels may be unreliable in sickle cell patients; therefore the use of the therapeutic index is less helpful in this group. The trend in ferritin level may be a useful indicator of iron stores and chelation efficacy. In general patients should also be monitored with T2*MRI and R2 MRI (a magnetic resonance imaging method used to determine cardiac and liver iron burden) however clinical evidence suggests that Sickle cell patients are less likely to have cardiac iron deposition.

Thalassaemia major patients:

Transfusion dependent Thalassaemia major patients have both high gut absorption of iron as well transfusional iron; the majority of these patients will transition from the paediatric service already established on chelation therapy. However the occasional patient will present as adult either inadequately chelated, (usually due to migration), and need to be commenced on chelation. In such cases urgent assessment of the Iron burden must be undertaken as well as full discussion about all the available chelators. If there is cardiac compromise Desferrioxamine as per Appendix 1 must be commenced. Otherwise the choice of chelator should be the result of a decision taken between the patient and clinician taking into account current iron stores as evidenced by serum ferritin levels, liver/heart iron burden assessment, trends in ferritin levels and patient choice.

Thalassaemia intermedia patients:

Thalassaemia intermedia patients usually require transfusion only occasionally but there is evidence of iron accumulation even in the untransfused patients. Hence these patients iron burden must also be monitored. The choice of chelator for these patients should be the result of a decision taken between the patient and an experienced clinician taking into account taking into consideration the same factors as for thalassaemia major patients.

Other inherited anaemias

Deferasirox has specifically been studied in adults and children with rare anaemia diagnoses who are transfusion dependent and would be a suitable alternative to Deferiprone. The risk of agranulocytosis and other cytopenias with Deferiprone appears to be increased in patients with Diamond Blackfan anaemia and should be used with caution in these patients

The licensed drugs:

○ Deferasirox :

Licensed as a first line agent in adults with thalassaemia.
Confirm normal renal function then start at 20mg/kg/day
See appendix 1 for protocol on prescribing Deferasirox

○ Desferrioxamine:

Licensed for all ages
Adult dose is 30- 50 mg/kg/day as a 12 hour infusion 3-7 nights/week.
See appendix 2 for protocol on prescribing Desferrioxamine

○ Deferiprone:

Initial dose 25/mg/kg tds (better tolerated if started once daily and then built up over 4 weeks). Dose may be increased up to 100mg/kg/day.
See appendix 3 for prescribing protocol

Combination therapy:

Desferrioxamine, as above, 2-6 infusions/week **plus** Deferiprone, as above, 7days/week
This is not a life-long treatment and is intended as intensive chelation to reduce iron stores rapidly and reliably. There is no experience of Desferrioxamine in combination with Deferasirox: this is NOT recommended. Desferrioxamine frequency should be decreased as ferritin level falls. Patients with consistent ferritin levels below 1000 should be considered for Desferasirox monotherapy.

Monitoring while on therapy

All patients on iron chelation require careful monitoring:

- Monthly biochemistry (creatinine and liver function tests)
- 3 monthly Serum ferritin
(Ferritin levels may be inconsistent, especially in sickle cell patients, so decisions must be based on trends over time)
- Cardiac T2* MRI must be carried out:
 - every 2 years if the T2* is > 20 ms and ferritin maintained at <1000micrograms/L on chelation
 - every year if T2* is > 20ms but ferritin >1000micrograms/L
 - at least every year if T2* is between 10-20ms
 - 6 monthly if T2*< 10 ms
 - 3 monthly if T2*< 10 ms and any evidence of cardiac impairment
- Once yearly Ferriscan of liver
- Annual audiometry and ophthalmology review
- Additionally, patients on Deferiprone require
 - careful monitoring of neutrophil counts - preferably weekly at commencement of therapy
 - education about the risk of agranulocytosis and
 - a letter to present to A&E if unwell with fever.
- Review the choice of chelator and doses at 6-12 month intervals.

Adjustment of iron chelation dose

This will be based on results of the above investigations and agreed with the patient. A copy of the clinic letter to the GP detailing the change should be sent to the patient.

- **Patients with normal or moderately raised iron stores:**

Serum Ferritin consistently <750micrograms/L

In sickle patients on exchange (rather than top up) transfusion and untransfused thalassaemia patients, monitor ferritin and consider stopping chelation if ferritin consistently <500micrograms/L and no other evidence of iron loading on Cardiac T2* MRI or Liver Ferriscan.

- **Patients with acceptable iron stores:**

Serum ferritin consistently 750-1500 micrograms/l

Liver iron (if available) 3-7mg/g dry weight

Cardiac T2* MRI >20 m sec

Continue current regimen and offer means to improve ease of treatment (if on Desferrioxamine ensure therapeutic index <0.025 please see appendix 2)

Discussion of alternatives if current regimen not tolerated

- **Patients with high iron stores:**

Serum ferritin consistently > 1500 micrograms/L or increasing trend

Liver iron >7 mg/g dry weight- by Ferriscan

Cardiac T2* MRI >20 m

All Patients on Desferrioxamine or Deferasirox

Optimise dosage and adherence (if on Desferrioxamine ensure therapeutic index <0.025 see appendix 2)

Consider switch to alternative chelator (or combination therapy in thalassaemia patients)

For thalassaemia patients on Deferiprone or combined Deferiprone and Desferrioxamine

Increase Deferiprone dosage up to 100mg/kg/day and/or increase frequency and dosage of Desferrioxamine, keep therapeutic index <0.025

- **In thalassaemia patients with increased cardiac iron (Cardiac T2* <20 milliseconds)**

High body iron stores: Serum ferritin consistently >1500 micrograms/l and/or liver iron >7 mg/g dry weight

Switch to combination Desferrioxamine 40-50mg/kg 2-5 days/week + Deferiprone 75-100mg/kg/day every day

Monotherapy with either Desferrioxamine or Deferiprone can be resumed once serum ferritin and liver iron have reduced to levels associated with mild iron loading.

Acceptable body iron stores: Ferritin consistently 500-1500 micrograms/l, and liver iron <7 mg/g dry weight)

Switch to Deferiprone 75-100mg/kg/day seven days per week

Chelation in iron-induced cardiac failure

Consider other contributory factors

All patients should be managed jointly with a cardiologist

Standard therapy is continuous i.v. Desferrioxamine 50-60 mg/kg/day

If this is not tolerated second line therapy is combination Desferrioxamine 40-50mg/kg s.c. infusion over 12-24 hours (or 24 hours IV) 5-7days per week plus Deferiprone 75-100mg/kg/day seven days per week.

Whichever chelation option is used, cardiac function may recover relatively rapidly, but patients will need to comply with an appropriate chelation regime over several years for reversal of cardiomyopathy and normalization of cardiac iron levels.

Appendix 1: PROTOCOL FOR DEFERASIROX (EXJADE)

Indication

Deferasirox (Exjade), a once daily oral iron chelator, is licensed in the UK for the treatment and prevention of iron overload (transfusion haemosiderosis) in both adult and children over 2 years.

Dosage

Recommended starting dose – 20mg/kg

To maintain iron balance give 10mg-20mg/kg

To reduce iron burden 20mg-30mg/kg

Treatment should be started by a consultant haematologist after approximately 20units (about 1000mL/kg) of packed red blood cells or when serum ferritin levels >1.000micrograms/l

Administration

Exjade should be taken once a day at approximately the same time each day, preferably morning and not with any antacids. It is administered orally as a tablet that is dissolved in 100-200mL of water, orange or apple juice. (It must not be dissolved in fizzy drinks).The tablets come in 125mg, 250mg, or 500mg doses. Exjade is mainly excreted in the faeces (about 84% of the dose) t½ ranges from 8 to 16 hours

Monitoring

	Test required
Before starting Exjade	Serum ferritin Serum creatinine x2 Creatinine clearance x2 Proteinuria Liver function tests
1st month of treatment	Serum creatinine (weekly) Creatinine clearance (weekly)
After Dose adjustment	Serum creatinine Creatinine clearance
Monthly	Serum creatinine Creatinine clearance Liver function tests (<i>more often if clinically Indicated</i>)
Monthly(In transfused patients) 3 monthly in untransfused	Serum Ferritin
Yearly	Audiometry and Ophthalmic review

Dose adjustment

Exjade can cause a rise in serum creatinine and liver transaminases in some patients. The dose adjustment must be based on the results of monitoring and made in 5-10mg/kg steps to fit both the patient's response and therapeutic goals. In adults the daily dose can be reduced by 10mg/kg if serum creatinine rises >33% above pre-treatment measurements on 2 consecutive visits and no other cause can be found.

After dose reduction, monitor patient closely; if serum creatinine rises further an interruption of treatment is recommended. Treatment should only be re-initiated after review with Consultant haematologist. If despite reduction and interruption, levels remain elevated and there is any other abnormality of renal function, the patient should be referred to the joint sickle renal investigation.

Side Effects

	Side effect	Action
Expected	GI disturbances- nausea, vomiting, diarrhoea, indigestion, constipation	Treat symptomatically do NOT stop treatment
Common	Increase in creatinine and transaminases, headache, abdominal distension, proteinuria	See dose adjustment
Rare	Anxiety, dizziness, early cataract, hearing loss, gastritis, hepatitis, pigmentation disorder, pyrexia, fatigue, oedema, glycosuria	

Blood tests 6-8 weekly once stable

Minimum 6 monthly reviews including annual review

Appendix 2: PROTOCOL FOR DESFERRIOXAMINE (Desferal)

Desferrioxamine is used infrequently at Guys and St Thomas so notice must be given to the pharmacy department to organise disposable infusional pumps and Sickle ANP and CNS team must also be given notice so they can organise training and education for the patient+/-carers on how to use the pump.

All patients must be referred for audiology and ophthalmological review **before** commencing Desferrioxamine

Indication;

Desferrioxamine is commenced by an experienced Consultant Haematologist when a patient is assessed as iron overloaded based on serial serum ferritin >1000 microgram/l, and or MRI assessment of Liver and or cardiac iron burden confirming iron overload. The starting dose will depend on serum ferritin level.

Dosage and Administration

Desferrioxamine is prescribed as Desferal and is administered as a subcutaneous infusion over 10-12 hours (usually overnight), typically over 5 nights a week. The frequency and duration of infusions should be tailored to patient's need and adherence. Lowest effective dose should be used.

Intravenous Desferrioxamine is given as a continuous infusion over 24 hours via an in-dwelling venous catheter.

Suggested doses based on a 7 night infusion programme: (increase accordingly if used for <7nights)

Ferritin	Desferal dose (7nights)	Desferal dose (5 nights)
<2000	25mg/kg/day	35mg/Kg/day
2000 – 3000	35mg/kg/day	49mg/Kg/day
>3000	Up to 50mg/kg/day	70mg/Kg/day

- A target ferritin of below 1000micrograms/l is recommended in thalassaemia major.
- A ferritin level of less than 2500micrograms/l is associated with decreased cardiac complications.
- Usual dose is between 20-40mg/kg/day. (Maximum dose is 50mg/kg/day, but a dose of 40mg/kg on 5 nights a week is usually adequate if compliance is good).

Dose adjustment:

The therapeutic index is calculated as the mean daily dose of Desferrioxamine in mg/Kg divided by the serum ferritin level in micrograms/l; in a patient on 45mg/Kg of Desferrioxamine 5 nights per week who has a serum ferritin of 2500micrograms/l, the therapeutic index is calculated thus:

$$\text{Mean daily dose: } 45 \times 5 \div 7 = 32.14$$

$$\text{Therapeutic index: } 32.14 \div 2500 = 0.0128$$

Aim is to keep the therapeutic index < 0.025 to avoid over chelation of patients

As ferritin levels fall, if the therapeutic index exceeds 0.025, the dose of Desferrioxamine should be decreased. Serum ferritin should be monitored 3 monthly and Desferrioxamine doses reviewed at 6 monthly.

Complications

- Pyrexia
- Swelling/irritation at injection site: add 1-10mg of hydrocortisone to syringe if a major problem
- Severe allergy is rare but can occur so **give the first dose in hospital.**
 - *Desensitization is usually successful.*
- Sudden intravenous boluses can lead to nausea, vomiting or hypotension and collapse.
- Deafness is uncommon when doses are kept within guidelines but can occur with prolonged treatment and higher doses usually high frequency sensorineural hearing loss. If abnormal audiogram, stop Desferrioxamine. Consider recommencement when audiogram normal with close Audiology supervision.
- Vision disturbance: stop Desferrioxamine immediately if any visual disturbance is reported. If recommenced do so at a lower dose with close ophthalmological observation
- Pulmonary toxicity: acute respiratory distress syndrome has been described following treatment at excessively high doses – do not exceed recommended doses
- Pregnancy: safety of Desferrioxamine not established STOP when pregnant. If heavy iron burden consider low doses from 18th week gestation
- Safe whilst breast feeding
- Haematological abnormalities such as thrombocytopenia, neutropenia and eosinophilia reported
- Care should be taken when in combination with psychotropic drugs there are reports of coma with concurrent administration of phenothiazine derivatives.
- Infections
 - Yersinia infections stop Desferal and treat with ciprofloxacin
 - Mucormycosis and Pneumocystis carinii : stop Desferrioxamine: (may be due to suppressant effect of Desferrioxamine on Lymphocytes)

Monitoring

- Yearly audiogram
- Yearly ophthalmology
- Monitoring for complications of iron overload

Special situations:

Continuous IV Desferrioxamine has to be by a central line (Permanent central line for treatment > 5days). Indications for IV continuous Desferrioxamine are:

- Acute or chronic cardiac problems due to iron overload
- Early cardiomyopathy detectable by echo or other method, *even in absence of clinical symptoms or signs*
- Poor compliance with sc Desferrioxamine and inadequate chelation
- Women with ferritin > 2500 who plan a pregnancy

Given as 5-6 infusions over 10-12 hours per week using an infusion pump
Provision of infusion pumps will need to be organised via pharmacy.

Appendix 3: **PROTOCOL FOR DEFERIPRONE (Ferriprox)**

Indications

Treatment of iron overload in patients with Thalassaemia major for whom Desferrioxamine therapy is contra-indicated, or have serious toxicity with Desferrioxamine therapy or whom have expressed a preference for Deferiprone

Treatment of iron overload in patients with Thalassaemia major or sickle cell disease, in conjunction with Desferrioxamine to improve iron chelation

Dosage and Administration

Deferiprone therapy should be initiated and maintained by a haematology consultant

Dosage is 25mg/kg body weight, oral use, three times a day, for a total daily dose of 75mg/kg/day. Dosage should be rounded down to the nearest half tablet (produced as Ferriprox 500mg tablets, these can be halved)

Dosages above 100mg/kg/day are not recommended

In poor responders higher doses or combination therapy with Desferrioxamine should be discussed with the haematology consultant

Contra-indications

- Hypersensitivity to the active substance or any of the excipients
- History of recurrent episodes of neutropenia
- History of agranulocytosis
- Pregnancy or breast-feeding
- Patients should not take any other medication which is known to be associated with neutropenia or which can cause agranulocytosis (eg. Hydroxyurea)

Complications

- Neutropenia/Agranulocytosis (occurs in 4%/1% cases respectively), reddish-brown discoloration of urine, nausea and vomiting, abdominal pain, increased appetite
- The gastrointestinal side-effects are more frequent at the beginning of therapy and usually resolve within a few weeks without the discontinuation of treatment. In some cases the dose can be reduced and gradually increased.
- Arthropathy range from mild pain to severe arthritis, spontaneously recover occurs despite continuing therapy. Increased ALT values usually asymptomatic and transient and ALT returns to normal without discontinuation or dose decrease. Zinc deficiency

All patients must be advised to report to their physician any symptoms indicative of infection such as fever, sore throat and flu like symptoms.

Monitoring

1. Weekly full blood count
2. Monthly ferritin level
3. Monthly zinc level (replace if low)
4. Monthly U+Es and LFTs (including ALT)

Management of neutropenia/agranulocytosis (neutrophil count $<1.5 \times 10^9/l$)

- stop Deferiprone
- repeat full blood count daily, until recovery
- after recovery check counts weekly for three more weeks
- if there is evidence of infection, appropriate investigation and antibiotics should be instigated

- consider G-CSF, and protective isolation if the neutrophil count is $<0.5 \times 10^9/l$

If neutropenia is confirmed, Deferiprone therapy should be re-initiated only if absolutely necessary and if there is intensive monitoring of blood counts. Deferiprone should be permanently discontinued if there is severe neutropenia (neutrophils <0.5).

Special warnings and special precautions for use of Deferiprone

- Deferiprone is not recommended in HIV positive or in immunocompromised patients
- Deferiprone is renally excreted so there may be an increased risk of complications in patients with impaired renal function
- Deferiprone is metabolised in the liver, so care must be taken in patients with hepatic dysfunction. If there is a persistent rise in ALT, interruption of deferiprone therapy must be considered
- The safety of concurrent use of Vitamin C has not been established and caution should be used when administering concurrent Vitamin C
- Women of childbearing potential should be advised to avoid pregnancy and to use adequate contraception. If they become pregnant, Deferiprone should be immediately stopped
- Treatment should be stopped if ferritin levels fall to $<500\mu g/l$

References

Management of Iron chelation therapy in transfusional iron overload for Thalassaemia, sickle cell and inherited anaemia. Dr Kate Ryan, Central Manchester Children's hospital

UK Forum for haemoglobin disorders: Consensus view on choice of iron chelation therapy in transfusional iron overload for inherited anaemias 2007. UK Thalassaemia society standards for care 2008

Exjade[®], (2006) Summary of product characteristics

Desferal Summary of product characteristics