

Guidelines for Iron Chelation Therapy in Children and Young People receiving regular Blood Transfusions

Introduction

This clinical guidance covers iron chelation therapy in:

- Patients with transfusion-dependent thalassaemia
- Sickle cell disease patients on regular transfusion
- Any other patients on a regular transfusion programme

Iron accumulation occurs in transfusion dependent individuals as every unit of blood contains approximately 200mg of iron, which cannot be excreted. Transfused iron accumulates in endocrine organs, liver and heart and will cause severe morbidity and early death if untreated.

Scope

This clinical guidance is for hospitals in the Wessex and Thames Valley Haemoglobinopathy Network. Please see national guideline

<https://onlinelibrary.wiley.com/doi/10.1111/bjh.17839>

When to start iron chelation

- Decision is based on individual factors but is considered when Ferritin $>1000\text{micrograms/l}$ or after 10 units blood. Ensure correct amount of blood is transfused by measuring pre transfusion haemoglobin which should be $>$ and close to 95g/l.
- Decision to start iron chelation should be discussed with a Consultant paediatric haematologist at specialist centre. The drug can be prescribed and dispensed from the local hospital. Dose changes can be discussed with the specialist centre if uncertainty.
- The decision about which drug to use is influenced by the age of the child, parental and child preference and concomitant clinical findings.
- Patients are monitored locally and at their annual review by consultant paediatric haematologist at The Children's Hospital, Oxford (CHOX).

Available medications

According to UKTS (UK Thalassaemia Society) National standards

- **Age 2-5 yrs.**
 1. Should start on Desferrioxamine (Desferal®) infusions once ferritin is $>1000\mu\text{g/l}$
 2. Offer Deferasirox FCT (Exjade®) if unable to tolerate infusions
- **Age 6 years or older**
 1. Offer Deferasirox
 2. Use Desferrioxamine if side effects such as renal impairment, deranged liver function tests or unable to tolerate Deferasirox

Desferrioxamine (Desferal®) in major Haemoglobinopathies**Dose Range**

- 20-50mg/kg infused 5-7 times a week over 8-12 hours SC/IV
- Ascorbic Acid orally on days of chelation may increase urinary iron excretion. Higher doses or doses taken on non Desferrioxamine days may precipitate cardiac dysfunction. Ascorbic Acid should be given only if the patient is receiving Desferrioxamine regularly and should not be administered within the first month of Desferrioxamine therapy.

Administration

There are a variety of pumps available for administration of Desferrioxamine.

- Baxter infuser – disposable pump used for weekly continuous iv dosing.
- CADD – cassette filled with Desferrioxamine. Used for intermittent iv or sc dosing over a course of a week.
- Graseby – vials of 2gm of 500mg of Desferrioxamine are dispensed for the patient to reconstitute their own drug each night into a syringe. This is an option for intermittent sc doing only. However due to the fact that patients must make their own drugs, this is the least preferred option and should be discouraged.
- Parents /patients will be trained to self administer at home

Relative Contraindications

1. Pre-existing sensory neural hearing loss.
2. Pre-existing macular retinal pigment epithelial disease.
3. First trimester of pregnancy.

Baseline Investigations

- Liver function, renal function, ferritin
- Baseline ophthalmology and ENT assessment.

Monitoring

- Every three months – liver function, renal function, ferritin
- Annually – ENT, ophthalmology review, cardiac T2* MRI scan (after 8 years) .

Administration in Presence of Cardiac Siderosis

- Prescribe highest tolerated daily dose, based on LIC and therapeutic index.
- Administer 7 days/week, each infusion lasting minimum 14 hours/day.
- If symptomatic cardiac disease, LV EF <50%, or cardiac MRI T2* <8ms, administer full continuous infusion in combination with oral iron chelator (Note that indwelling venous catheters will require full anticoagulation for VTE prophylaxis).

Dose Adjustment for Adverse Effects

- Therapeutic (Porter) index: (Thalassaemia major only).

Mean daily dose (mg/kg) / ferritin (mcg/l). Aim to target the index <0.025 at all times.

- Febrile illness or diarrhoea: Consider Yersinia
 - 1. Symptoms : Abdominal pain, vomiting and or diarrhoea
 - 2. Interrupt Desferrioxamine
 - 3. Drug of choice : Ciprofloxacin
- Local skin reaction
 - Ensure correct dilution (e.g. 10% solution) and rate of infusion. Check for dressing allergy.
 - If ulceration of skin, ensure adequate depth of needle insertion. Addition of Hydrocortisone to infusions.
- Severe allergy
 - Consider desensitisation protocol or alternative iron chelator.
- Audiology
 - If worsening symptoms of hearing loss or tinnitus or progressive deterioration noted pure audiometry, withhold Desferrioxamine and repeat audiogram every three months until deficit has stabilised before reintroducing chelation. Base reintroduction dose on reassessment of hepatic iron concentration, Porter index or the previously tolerated dose.
- Vision
 - If worsening symptoms of visual loss (especially night blindness or central scotoma) or new lesions noted in an ophthalmic assessment consistent with chelator toxicity, hold off Desferrioxamine until symptoms and ophthalmic findings have completely resolved. Base reintroduction of dose on the above variables.

Deferasirox FCT (Exjade) in major Haemoglobinopathies**Indication**

Deferasirox (FC) should be considered first line therapy for all patients for all children > 2 years old with major Haemoglobinopathies requiring chelation therapy

Dose Range

7-28mg/kg/day in single daily dose

It is available in 3 tablet strengths (90, 180 and 360mg) and the tablet should be swallowed whole with water or crushed and sprinkled on soft food, such as apple puree. It should be taken at the same time every day on an empty stomach or with a light meal.

Relative contraindications

- Avoid if estimated glomerular filtration rate less than 60 mL/min/1.73 m²
- Pre-existing severe liver disease

Baseline Investigations

- FBC, reticulocyte count
- LFT, Renal, Bone, CRP, Urinalysis
- Ferritin

Starting dose

- 14mg /Kg once daily according to serum-ferritin concentration and amount of transfused blood (consult product literature)
- Adjustments can normally be made in increments of 3.5-7 mg/kg every 3-6 months according to serum-ferritin concentration

Monitoring

- Initially monthly - LFT, Renal, Bone, CRP, Urinalysis
- 3 Monthly – Ferritin,
- Annually - Cardiac MRI T2* (when > 8 years)
- Annually – Ophthalmology and audiology review

Dose adjustments for Adverse Effects: Increase in serum creatinine

- If > 33%, >ULN or proteinuria > 0.3 on two occasions, reduce dose by 7mg/kg and repeat after 2-4 weeks.
- Discontinue if elevation persists and consider renal unit referral.
- Dose can be increased (in 3.5mg/Kg increments) if creatinine stable at <33% ULN for one month.

Elevated LFT's

- ALT/AST – progressive and persistent levels that can not be attributed to other causes, stop Exjade FCT
- Monitor weekly
- Consider re-challenging at reduced dosage when LFT's return to normal.

Skin rash

- Usually resolves without requiring dose reduction
- If severe, discontinue until rash settles and re-challenge with antihistamines.

Dose adjustment according to iron stores:

- This is indicated by increasing serum ferritin levels (>1500 μ g/L), increasing liver or cardiac loading or development of new clinical complications of iron overload.
Dose can be increased by 7mg/kg every month to a maximum dose of 28mg/kg.
In general, patients with high and increasing iron burden should be treated with alternative regimens.

- Once targets have been achieved for hepatic iron (< 2mg/g dry weight) and cardiac T2* (> 20ms), dosage should be maintained.
- If serum ferritin falls consistently < 500 µg/L then consider tapering the dose.

**Patient with High liver iron but no cardiac iron (Discuss with your specialist centre-
Oxford or Southampton)****Existing treatment Desferrioxamine**

1. Optimise doses and tackle compliance issues, consider adding in Deferiprone (clinical guideline available (<http://nssg.oxford-haematology.org.uk/oxford/red-cell/deferiprone-in-scd-thal.pdf>) as combination therapy if not previously used this in combination.
2. Consider switching to Deferasirox at an iron reducing dose.

Existing treatment Deferiprone

1. Optimise doses to 75-100mg/kg/day
2. Add in Desferrioxamine infusions as combination therapy on 1 to 5 days a week if patient is willing to use these according to severity of iron load. As liver iron burden falls gradually reduce the frequency of the Desferrioxamine infusions but aim to keep at least 1 to 2 infusions per week as iron burden will go up on monotherapy.
3. Switching to Deferasirox if patient is not willing to use Desferrioxamine infusions.

Existing treatment Deferasirox

1. Optimise dose going up to 28mg/kg/day if needed, tackle compliance if dose is optimal.
2. If despite optimal doses Liver iron not improving consider changing to Desferrioxamine infusions or combination therapy with Deferiprone and Desferrioxamine.

Patient with Myocardial iron loading but not heart failure: (Discuss with your specialist centre- Oxford or Southampton)**Existing treatment Desferrioxamine**

1. Optimise doses and tackle compliance issues, consider adding in Deferiprone as combination therapy if not previously used this.
2. Consider using Deferasirox at a 28mg/kg/day dose

Existing treatment Deferiprone

1. Optimise doses to 75-100mg/kg/day and tackle compliance issues.

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2. Add in Desferrioxamine infusions on 5 days a week if patient is willing to use these according to severity of liver iron load. As liver iron burden falls gradually reduce the frequency of the Desferal infusions but aim to keep at least 1 to 2.
3. Switching to Deferasirox if patient is not willing to use Desferrioxamine infusions.

Existing treatment Deferasirox

1. Optimise dose going up to 28mg/kg/day if needed, tackle compliance if dose is optimal.
2. If despite optimal doses cardiac iron not improving and liver iron is low, or patient developing renal toxicity then switch to Deferiprone monotherapy with careful monitoring.

Patient with myocardial iron and heart failure

1. Start on IV Desferrioxamine 24 hours a day 7 days a week along with all appropriate cardiac care. Keep on this regime until ejection fraction improves and patient stable.
2. Consider adding in Deferiprone, as combination therapy if patient is stable.

Contact Details

[PH1 Paediatric Hemoglobinopathy Team and Admission Procedures – Oxford and Southampton.](#)

References

Understanding Exjade FCT Novartis October 2016.

www.emc.medicines.org.uk: SPC for Desferal vials. Novartis. Last updates on eMC 2/7/14
BNF for Children March 2015

UKTS. The Treatment of Iron Overload. <http://ukts.org/living-with-thalassaemia/treatment/chelation.html>

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Review

Name	Revision	Date	Version	Review date
Amrana Qureshi	Routine Review	July 2021	2.3	July 2023
Manuela Sultanova	Inclusion of Introduction, Scope, Autor Review table. Updated logo and formatting.	Nov 2021	3.0	July 2023
Amrana Qureshi	Routine Review	August 2022	3.1	August 2024