Transfusion Dependent Thalassemia (TDT) Chelation Guidelines

Goals of Chelation

1. Maintain an even balance of iron going in via red cell transfusions and iron being excreted through chelation.
2. Prevent deposition of excess iron from transfused red cells into tissues. The liver is the normal storage organ for iron and very little iron is deposited in other tissues as long as the liver can safely store iron. Once the capacity of the liver is exceeded, it can deposit in other organs and cause those organs to have impaired function. These organs include the heart and endocrine organs such as the pituitary gland, the pancreas, the testes and ovaries.
3. Maintain low tissue iron concentrations as measured by MRI. Goal: liver iron concentration (LIC): 3-7 mg/g dry weight (DW), and myocardial iron by T2*: greater than 20 milliseconds. Ferritin levels are used to follow trends only and chelation decisions are made only based on MRI levels.
4. If iron has already been deposited in tissues other than the liver, more intensive chelation will facilitate the removal of this iron, so as to minimize the risk of tissue dysfunction as a result of iron toxicity.

Beginning Chelation

- It is important to begin chelation appropriately so as to prevent tissue iron deposition. Ideally, in order to achieve and maintain iron balance, chelation should be started when the LIC goes above ~7 mg/g DW. Chelator medications are approved for use in children above the age of two years.
- In children who have been transfused from infancy, the goal is to begin chelation when the child turns ~two years of age. An MRI is performed to determine the baseline LIC. The LIC value will usually be above 10 mg/g DW from calculations based on published data, and chelation should be initiated.
- At our center, the starting chelation regimen is single-agent oral chelation. Typically, we will start deferasirox (Exjade®) at 20 mg/kg once a day.
- In older children and adults who have started regular transfusions later, the LIC is measured by MRI after ~12 transfusions. Once the LIC is confirmed to be above the desired range, i.e. >7 mg/g DW, chelation is begun with deferasirox (Exjade®) at 20 mg/kg once a day, or deferasirox (Jadenu®) at 14 mg/kg once a day.
- For patients who do not tolerate deferasirox in either form, either because of changes in liver or kidney function or GI side effects, deferiprone (Ferriprox®) may be used at 75-100 mg/kg/day, divided into three doses daily. Alternatively, desferrioxamine (Desferal®) may be used at 30-50 mg/kg by subcutaneous infusion five – six nights/week.

Monitoring Efficacy of Chelation

- Monitoring the efficacy of chelation is important to prevent excessive buildup of iron which may cause organ dysfunction. Because chelation efficacy is determined in great part by compliance with the chelation regimen, monitoring also provides a good indicator for chelation compliance.
- Compliance must be reinforced at every visit.
- The gold standard for assessing body iron burden and its monitoring is MRI of the liver and heart.
- LIC is measured by MRI at the initiation of chelation and then annually thereafter. The goal is to maintain LIC of 3-7 mg/g DW.
- Myocardial MRI for T2* measurement is usually not performed until age 10 in patients who have started chelation appropriately and who have not had high LIC values at any time. The goal is maintenance of myocardial T2* of greater than 20 milliseconds. For patients with good chelation compliance and steady LIC values in the desired range, myocardial T2* studies may be performed less frequently – ~every two years.
- Serum ferritin levels are also monitored. However, this is only helpful in following trends and is not used by itself to make decisions related to the chelation regimen. Serum ferritin levels are elevated when there is inflammation, and may cause alarm, but LIC does not usually rise. If serum ferritin levels show an upward trend in the absence of inflammation, an MRI should be performed to check LIC, and, if elevated, chelation may be intensified.

Monitoring Chelator Toxicity

- Deferasirox – common adverse effects include GI upsetment, to which the patient is often tolerized. These effects are not seen as often in patients with Jadenu®. More significantly, there may be elevations of serum creatinine or AST/ALT. These are usually dose-dependent, and require modification of the dose or change of medication. Liver and kidney function (including urine for b2 microglobulin) is checked at least once per month – usually at the time of transfusion. For patients who can only tolerate lower doses of deferasirox, a second agent may need to be added – usually deferiprone or desferrioxamine, three – four days per week.
- Deferiprone – major side effects include neutropenia, with rare agranulocytosis, where the neutrophil count falls and makes the patient susceptible to infection. This requires regular monitoring of white blood cell counts – initially every week, but may be spaced out to every two – three weeks once the patient is on a stable regimen and has had stable counts. If neutropenia occurs, dose reduction or cessation of the agent is necessitated. The other significant side effect is arthritis, with joint swelling and pain – this usually requires switching to another agent.
- Desferrioxamine is usually well tolerated, but may result in some local injection site pain and sterile abscess formation which could become secondarily infected. Patients must watch out for these effects and must rotate sites daily to minimize

risk and ensure adequate absorption of the drug. Desferrioxamine patients may also develop hearing loss, and occasionally tinnitus. Annual monitoring by audiogram is recommended. An annual eye exam is also recommended to monitor for retinal changes.

Chelation Intensification

Indications

a. Rising LIC year after year
b. LIC >15 mg Fe/g dry weight, with T2* >20 milliseconds, and no clinical cardiac disease
c. LIC 3-15 mg Fe/g dry weight, with T2* 10-20 milliseconds, and no clinical cardiac disease
d. LIC >15 mg Fe/g dry weight, with T2* 10-20 milliseconds
e. LIC 3-15 mg Fe/g dry weight, with T2* <10 milliseconds

Regimen

For a, b and c above:

- Increase dose of current chelation – Exjade® from 20 to 30 or 40 mg/kg/day, Jadenu® from 14 to 21 or 28 mg/kg/day.
- Reinforce compliance and reiterate the risks of elevated LIC and cardiac disease.

For d and e above:

- Add a second chelator. For those on deferasirox or deferiprone, usually add desferrioxamine 30-50 mg/kg three – four nights per week
- Alternatively, a combination of the two oral chelators has also been used with positive published results.