

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Oral Iron Chelators in the Treatment of Hematologic Diseases

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H&O What is the history behind the development of oral iron chelators?

AVH Until 1976, there was no established satisfactory treatment for removing iron from patients receiving multiple blood transfusions for refractory anemia, particularly thalassemia major. In 1976, the iron chelator deferoxamine (Desferal, Novartis) entered routine clinical practice.

Deferoxamine is not orally active and is given by subcutaneous infusions, generally in a schedule of 12 hours per day for 5 days per week. Patients are required to set up their own infusion including preparation of the agent from powder in a vial. The drug causes both urine and stool iron excretion. Early studies showed that as long as patients adhered to this schedule, deferoxamine was associated with an improved life expectancy, with a dramatically decreased incidence of death from heart disease due to iron overload.

It was also observed, however, that many patients did not comply with this demanding schedule. Teenagers particularly had a difficult time preparing the drug and infusing themselves 5 days per week. Many patients would decrease the number of weekly infusions or miss several weeks at a time. Studies in the United States and Europe showed that patients who complied with the prescribed therapy had a better life expectancy than those who did not. Further, even among compliers, some patients who were infusing the drug 5 days per week still encountered clinical problems including cardiac failure from iron overload. Moreover, for some patients, the drug proved unacceptable due to hypersensitivity. Toxicities associated with deferoxamine include adverse effects on sight and hearing and on bone development and growth in

children. What was needed, therefore, was a second agent that could be taken by mouth (thus avoiding the daily infusion requirement), would have few severe side effects, and would be equally or more effective at removing iron and less expensive.

H&O What was the first oral iron chelating agent approved?

AVH The first and only currently licensed oral iron chelating agent is deferiprone, marketed by Apotex as Ferriprox and by Cipla in India as Kelfer. This drug was first used in patients in 1987 and is now licensed in approximately 45 countries for patients in whom deferoxamine for one reason or another is unsatisfactory. It is still not approved for use in North America. Deferiprone has a lower molecular weight than deferoxamine and can be absorbed without being broken down by the gut. The drug causes iron excretion almost exclusively in the urine. Recent studies have shown deferiprone is particularly effective at removing heart iron.

H&O Are there other oral chelating agents in development?

AVH ICL670 (deferasirox, Exjade, Novartis), another oral agent, is currently in phase III clinical trials and has been granted priority review status by the US Food and Drug Administration. With this agent iron is eliminated through the bowel. Studies have shown it to be effective at reducing liver iron and thus body iron burden. No studies regarding the effect of ICL670 on cardiac iron have been reported. Another agent, GT56-252 (Deferitrin, Genzyme) is in early clinical development.

H&O What toxicities are associated with deferiprone?

AVH A number of side effects were noted early in the development of deferiprone, including agranulocytosis (the temporary loss of white blood cells), which can be dangerous since infections may supervene. Additional side effects include joint symptoms, nausea, and other gastrointestinal symptoms. A minor side effect is zinc deficiency, observed in some patients with diabetes. According to studies evaluating the incidences of these

adverse events, approximately 1 in 100 patients experiences agranulocytosis, 1 in 20 experiences arthropathy, and 1 in 10 experiences nausea and other gastrointestinal symptoms. Overall, in clinical studies the dropout rate due to these known side effects has averaged approximately 10–15%. Early studies noted abnormal liver function in some patients, particularly those with hepatitis C, but these changes were not permanent.

H&O What has prevented US regulatory authorities from approving this drug?

AVH Controversy regarding deferiprone began in 1998 when a paper was published in the *New England Journal of Medicine* by a Canadian group suggesting that the agent caused liver fibrosis and with time lost efficacy as a chelating agent. The evidence for the association with liver fibrosis in this study was poor. Among the 5 patients in whom the drug was said to be associated with liver fibrosis, 4 had hepatitis C, which can itself cause liver fibrosis, and all 5 had iron overload. Moreover, some histopathologists did not find an increase in fibrosis even in these 5 patients. A much larger study published 4 years later with 56 repeat biopsies of patients who had been taking deferiprone for 3 years found no histologic evidence that it caused liver fibrosis. No other groups have reported evidence of this side effect. Regarding the reported lack of efficacy, the dose used in the study was 75 mg/kg. More recent studies have been using a dose of 100 mg/kg, which appears to be optimum for many patients. With deferiprone, the amount of iron eliminated is very closely related to the dose of the drug. The optimum dose may differ between patients.

Recent randomized and nonrandomized retrospective and prospective studies of patients treated with deferiprone show lower cardiac iron levels and fewer cardiac deaths than are observed with patients treated with deferoxamine. The death rate from cardiac failure associated with iron overload in thalassemia has dramatically decreased in countries (eg, the United Kingdom, Italy, and Cyprus) where deferiprone is prescribed but has not decreased in North America, where deferiprone is not used.

H&O Would the iron chelating agents be used in combination?

AVH Deferiprone has been used in combination with deferoxamine since 1998. A common regimen involves taking deferiprone 7 days per week and if this is not sufficient to achieve a negative iron balance, then an additional “boost” of 2 days of deferoxamine is prescribed. Many patients who would be noncompliant with a 5-days-per-week infusion schedule will comply with infusing deferoxamine 2 days per week. The combination is effective.

The 2 drugs can be given simultaneously with no adverse drug-drug interactions. In fact, there appears to be some synergy between the 2 agents, in that more iron may be removed when they are given together than when they are given separately.

At some point combination therapy with 2 oral agents may be investigated. Since ICL670 removes iron from the liver to the stools and deferiprone removes iron particularly well from the rest of the body into the urine, the 2 may well work effectively together.

H&O Does the location from which iron is removed play a significant role in a patient's outcome?

AVH It has been hypothesized that if iron is removed from the liver, the body iron will be redistributed from the heart to the liver, in which case the location from which iron is removed would be inconsequential, as long as the iron is removed. It now appears the answer is not so simple. MRI studies show a poor correlation between heart and liver iron. Sometimes intensive chelation (24-hour intravenous deferoxamine) can improve heart function within weeks—long before body iron has changed. This may be through eliminating non–transferrin-bound iron from the plasma. This iron is particularly toxic. Once iron is in the heart, it can take a long time for it to be removed with deferoxamine. By contrast, iron can be removed much more quickly from the liver. Overall, it is essential to keep cardiac iron below a toxic level to prevent cardiac failure or arrhythmia.

H&O Is it possible for an iron chelator to remove too much iron?

AVH Iron balance can be monitored by measuring how much iron is being removed in the urine and stools. This measures how much iron is leaving the body in relation to how much has accumulated from blood transfusions. Iron status can be tested by measuring liver iron, although the procedure is complicated. Serum ferritin level is an inaccurate measure of iron status but is useful for measuring changes in iron burden. In the last few years, magnetic resonance imaging (MRI) techniques have been introduced that enable measurement of liver and cardiac iron, making it possible to more accurately monitor iron levels in patients. If the amount of iron leaving the body is greater than the amount entering the body through blood transfusions (approximately 0.25 g per unit of blood), then the patient is in negative iron balance. At low levels of body iron deferoxamine becomes particularly toxic to hearing, eyesight, and growth. On the other hand, deferiprone has not been found to have increased toxicity at low levels of iron burden.

H&O Is the oral agent proving to be more economical?

AVH In developed countries, where the government usually bears the burden of drug cost, the price of a drug is not that important for patients. However, in poor countries with a more limited health budget, there is a particular need for inexpensive compounds. Agents that need to be administered by infusion will involve greater costs than oral agents, since infusion requires syringes, needles, and tubing. As much as there is a need for cheap oral agents in developed countries, the need is even more dramatic in underdeveloped regions. Of course, the costs should be as low as possible.

H&O What other advantages does an oral chelating agent offer?

AVH Thalassemia major is not the only transfusion-dependent refractory anemia treated with iron chelators. Other conditions include those characterized by a low white cell count or a low platelet count, such as myelodysplasia. In these situations, an oral agent is beneficial since

inserting a needle increases the risk of infections as well as bruising or bleeding at the injection site. Also, having access to easy iron chelation can enable blood transfusion to be used with less fear of iron overload. In sickle cell anemia, for example, switching off hemopoiesis can be achieved with blood transfusions and consequent iron overload treated more easily with an oral agent than with subcutaneous infusions.

Suggested Reading

Anderson LJ, Wonke N, Prescott E, et al. Improved myocardial iron levels and ventricular function with oral deferiprone compared with subcutaneous desferrioxamine in thalassemia. *Lancet*. 2002;360:516-520.

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