# Transfusion-Dependent Iron Overload and MDS:

## A Handbook for Patients

Third Edition


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Many patients in the early stages of MDS experience anemia, a condition characterized by a persistently low hematocrit, a measure of the body's red blood cells, or persistently low levels of hemoglobin, a blood protein that carries oxygen to the body's tissues.

Roughly 80% of patients are anemic when they are initially diagnosed with MDS. Some anemic patients receive periodic blood transfusions as supportive therapy to help stave off the fatigue that usually accompanies anemia. Although chronic anemia is seldom life threatening, it can drastically reduce a patient's quality-of-life. Therefore, most clinicians recommend blood transfusions for patients with symptoms of anemia.

## Transfusions for Anemia

Anemic patients who are candidates for regular or periodic blood transfusions typically have pale skin and experience fatigue and shortness of breath. They include MDS patients in the International Prognostic Scoring System's low-risk group or intermediate-1 risk group who are severely anemic, with a hematocrit consistently less than 30% or hemoglobin levels less than 10 grams per deciliter of blood. Many MDS patients with low-risk or intermediate-1 risk disease require periodic or multiple transfusions. Such patients may be classified as having refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) under the World Health Organization system or the French-American-British system.[1,2]

The frequency of transfusions for anemic patients who need supportive therapy varies from patient to patient. Some patients may need red blood cell transfusions as often as once every 1 to 2 weeks whereas other patients may only need a transfusion once every 6 to 12 weeks. The frequency is dependent upon the patient's symptoms, hematocrit, or hemoglobin level in the blood.[1]

Supportive therapy with blood transfusions is helpful in treating anemia; however, there is a downside — red blood cells carry iron and, after repeated transfusions, a patient may end up with elevated levels of iron in the blood and other tissues. Iron overload is a potentially dangerous condition. Fortunately, it can be treated.

## Am I at Risk of Iron Overload?

Iron overload is not a risk unless you receive a series of transfusions, usually over several years, or after a total of approximately 20 transfusions, whichever comes first. In addition to developing iron overload as a result of multiple transfusions, MDS patients with sideroblastic anemia may develop iron overload as a result of excessive absorption of iron from food.[1]

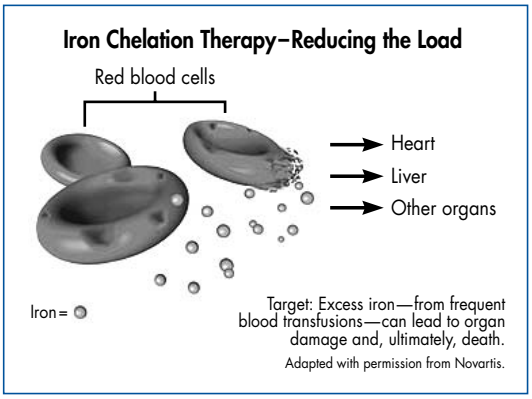
## What Exactly Is Iron Overload?

The frequency of blood transfusions varies by individual patients with anemia, depending upon symptoms and hematocrit or hemoglobin levels. However, the "typical" MDS patient with anemia who needs transfusion therapy will receive two units of blood every 2 to 6 weeks. Each unit carries about 250 milligrams of iron. Over the course of therapy, iron builds up in the body's tissues and organs, and after approximately 20 transfusions a patient may end up with toxic levels.[1,3]

Iron has powerful oxidant activity that can damage tissue. When excessive iron accumulates in the heart, liver, lungs, brain, bone marrow, and endocrine organs, the stage is set for a broad array of possible diseases and even life-threatening conditions, including heart failure, cirrhosis and fibrosis of the liver, gallbladder disorders, diabetes, arthritis, depression, impotence, infertility, and cancer.[3-5]

## How Is Iron Overload Treated?

For MDS patients who experience transfusion-dependent iron overload, two treatments are approved by the U.S. Food & Drug Administration (FDA) and available to patients by prescription: iron chelation, or iron removal, therapy with the drug Desferal® (generic name, deferoxamine) and Exjade® (generic name, deferasirox). Note that the spelling of the generic name of Desferal appears variably in the medical literature as deferoxamine, desferoxamine, and deferroxamine. In Europe and some other countries, but not in the U.S., another oral iron chelator, Ferriprox® (generic name, deferiprone), is available for patients with iron overload who are unable to use Desferal because of intolerability or lack of effectiveness. The three drugs *chelate*, or bind, to iron



and promote iron removal from the body.[4-12] MDS patients with anemia who require multiple transfusions and who receive iron chelation therapy have improved life expectancies.[6]

## *Desferal® (Deferoxamine)*

Considered the standard of care for removal of excess iron, Desferal is given in addition to blood infusion, and is administered by injection anywhere from 3 to 7 times a week. Some patients receive twice-daily subcutaneous (beneath the skin) injections of Desferal. Others receive slow intravenous infusion by way of a portable, battery-operated pump worn over a period of about 8 hours, often overnight. Desferal can also be given by injection into muscle (intramuscular administration).[4-7,9]

Patients can expect to receive up to two grams of Desferal for each unit of blood transfused. Typically, a physician will initiate treatment with one gram, gradually adjusting the dose upward until it reaches no more than three grams a day. Urine samples, which reveal how much iron the patient is excreting, help the physician adjust the Desferal dose to maintain a negative iron balance.[3,5,9]

Desferal is slow acting, removing only 6 to 10 mg of iron per infusion; however, it can maintain negative iron balance even when blood transfusions continue. Success depends on early initiation of therapy. If significant iron overload exists before chelation therapy is begun, the patient may succumb to progressive heart disease or fibrosis of the liver. Better timed chelation therapy, begun within two years of the initiation of repeated transfusions, can prevent or reverse these conditions.[3,5]

In addition to early initiation of therapy, patient compliance to the prescribed Desferal regimen is critical to the successful treatment of transfusion-dependent iron overload. Some patients discontinue Desferal iron chelation therapy because of the regimen's inconvenience or the discomfort of repeated needlesticks, particularly the hypersensitive reaction at the injection site. Patients should be strongly counseled and encouraged to continue treatment... because iron chelation therapy does prevent organ failure in patients receiving regular blood transfusions and does prolong life. Patients who feel they cannot tolerate the discomfort of needles should ask for a topical anesthetic cream, which can be applied an hour before the needlestick to alleviate pain. Many patients find intravenous delivery by way of a slow-infusion pump the most tolerable form of treatment because the needle remains in place for a week, eliminating the need for frequent needlesticks. Furthermore, intravenous chelation is more effective than subcutaneous chelation, often requiring fewer days of therapy.[5]

Research is continuing to explore ways to make Desferal more convenient and less burdensome for patients requiring multiple blood transfusions, including new transfusional methods.

## *Exjade® (Deferasirox)*

In late 2005, Exjade, formerly ICL670, was approved by the FDA, making this drug the first commercially available oral treatment for iron overload in the U.S.[6-8] Compared with the current standard of care, which often requires a subcutaneous infusion lasting eight to 12 hours per night, for five to seven nights a week for as long as the patient continues to receive blood transfusions or has excess iron within the body, Exjade is taken once daily at a dose of 20 milligrams per kilogram of body weight per day.[10] Exjade tablets are dissolved in a glass of orange juice, apple juice or water and taken as a drink. Completed phase III clinical trials in patients with beta thalassemia, sickle cell disease, other anemias as well as MDS have demonstrated that Exjade significantly reduced liver iron concentration (LIC), the accepted indicator for iron content in the body, and led to the maintenance or reduction of iron burden in transfused patients. LIC values above 7 mg of iron per gram dry weight (Fe/g dw) are associated with increased morbidity and mortality.

A recently published multicenter, randomized, phase III clinical trial of 586 patients with beta thalassemia, an inherited blood disorder in which patients receive regular blood transfusions, diagnosed with chronic iron overload compared the safety and effectiveness of Desferal and Exjade treatment.[11] More than two-thirds of the patients in this study had at-risk LIC. Participants received either Desferal infusions five days a week or drank Exjade dissolved in water each day before breakfast. Dosing of each drug was based on the patient's baseline LIC: patients with an LIC $\geq$7 mg of iron per gram dry weight (Fe/g dw) received higher doses than patients with an LIC $<$7 mg of iron per gram dry weight (Fe/g dw).

Exjade was found to be as effective as Desferal in patients receiving the highest drug doses, producing significant and similar dose-dependent reductions in LIC and serum ferritin, and effects on net body iron balance. A majority of these patients (approximately 60%), demonstrated sustained or reduced LIC levels during the study. However, in patients receiving the lowest drug doses, Exjade did not sustain or reduce LIC levels. This may have been due to the disproportionately lower doses of Exjade compared with the doses of Desferal given to patients with LIC $<$7 mg of iron per gram dry weight (Fe/g dw).[11] Additional clinical trials are ongoing, including one in low- and intermediate-risk MDS patients.

Novartis, the manufacturer of Exjade, has developed a program for patients taking Exjade called EPASS™ (**E**xjade **P**atient **A**ssistance and **S**upport **S**ervices) which includes prescription fulfillment, educational support, and reimbursement assistance. Another program, called Simple Steps, is available to help improve or reinforce compliance with the daily dosing of Exjade. As with all drugs, it is important to take Exjade as prescribed (once a day, every day) because the drug's effectiveness is related to the correct dosing.

## Other Iron-Chelating Drugs

In addition to Exjade, there is another oral iron chelator, Ferriprox® (generic name, deferiprone), that is licensed for use in Europe and other countries (but not the U.S.) for patients with iron overload who are unable to use Desferal because of intolerability or lack of effectiveness.[7,8,12] In clinical studies and in clinical practice, Ferriprox has been shown to be effective in removing iron from the body. Ferriprox has a side effect profile similar to that of Desferal.[8,12]

Another drug that is being tested is referred to as HBED (for hydroxybenzyl-ethylenediamine diacetic acid). Although it requires administration by injection, HBED appears to promote iron removal more efficiently than Desferal and therefore can be given less frequently or for shorter periods of time.[13]

## Can I Have an Adverse Reaction to Iron-Overload Treatment?

Some patients experience side effects while on iron chelation therapy with Desferal or Exjade.

Possible side effects of Desferal include bloody urine, blurred vision, rash, hives, itching, vomiting, diarrhea, stomach or leg cramps, fever, rapid heart beat, dizziness, or pain or swelling at the infusion site. Potential long-term adverse reactions include kidney or liver damage, loss of hearing, or cataracts.[3,5,9] The most common side effects associated with Exjade use (in clinical trials) include diarrhea, nausea, vomiting, headache, abdominal pain, fever, cough, and mild nonprogressive increases in serum creatinine.[10] Potential long-term adverse reactions to either Desferal or Exjade include kidney or liver damage, loss of hearing, or cataracts.[3,5,8,9,10,12]

Although rare, hearing and eye disturbances have been reported with Desferal and Exjade use. Therefore, patients should have an auditory test and an ophthalmologic exam prior to starting therapy and at regular intervals while on therapy. Your doctor should also measure your liver enzymes, kidney function, hematocrit, ferritin, and transferrin iron saturation percentage. You should report any adverse symptoms immediately to your physician, who will either adjust

your dose or, in case of severe abnormalities, discontinue treatment altogether. If severe reactions resolve, your physician may reintroduce iron chelation cautiously.[3,5,9,10] Again, the upside of iron chelation is the improvement in hematocrit and hemoglobin levels after being "de-ironed." MDS patients with anemia who require multiple transfusions and who receive iron chelation have a much reduced chance of toxic iron build-up in their organs and tissues and therefore have improved life expectancies.

## What Practical Measures Can I Take to Help Reduce Iron Overload?

In addition to iron chelation therapy for patients who experience transfusion-dependent iron overload, there are a few everyday guidelines you can follow to decrease your dietary intake of iron. To impede the absorption of iron, it helps to consume milk products, certain high-fiber foods, and tea. You should not eat raw shellfish, which may carry bacteria that can cause death in people suffering from iron overload. Last but not least, avoiding alcohol and tobacco smoke might help prevent further increase of iron levels.[3]

Most important, if you're receiving iron chelation therapy, be sure that your physician is closely monitoring iron accumulation in your tissues. If not, you are at increased risk of disease associated with iron overload. It is also critical that you comply with the iron chelation drug regimen. If you're feeling discouraged, don't give up—seek outside support. Help is available.

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