**Fatal congestive heart failure with deferiprone**

*Insuffisance cardiaque congestive fatale lors d’un traitement par déférisprone*

Aqodad et al. recently reported a fatal episode of congestive cardiac failure with sideroblastic anemia, followed by a bone marrow transplant in a patient that occurred in 2004 [1]. They suggested that deferiprone was responsible for the event because of the following elements:

- no pre-existing cardiac abnormalities were detected;
- the time relationship between deferiprone treatment and cardiac failure favoured the relationship;
- the absence of other apparent causes of cardiomyopathy.

However, as detailed below, the events cited by Aqodad et al. actually seem to provide evidence that the event was highly unlikely to have been caused by deferiprone.

Considering the patient’s history of long-term transfusion-dependency (240 red blood cell units transfused) and the severity of iron overload (serum ferritin up to 6360 μg/L and liver iron concentration up to 18 times the upper limit of normal), there is clear evidence of long standing generalized iron overload, placing him in danger of cardiac iron overload. Cardiac iron overload can occur in transfusion-dependent patients even in those who are apparently well-chelated with deferoxamine, as assessed by serum ferritin and liver iron concentrations [2]. There is no evidence that any iron which might have accumulated in the heart during the first period of blood transfusions in the late 1980s had been cleared with deferoxamine therapy, only that liver iron and serum ferritin values had declined. Similarly, it is unknown how much additional cardiac iron accumulation may have occurred due to the second series of transfusions in the late 1990s and early 2000s. Thus one must consider these events to have been important in predisposing the patient to heart failure. Although T2* may predict such an event, no cardiac magnetic resonance imaging assessment was reported. Echocardiogram, on the other hand, which was performed, is not likely to detect iron-induced toxicity and iron-induced cardiac failure, prior to the event [3].

The time relationship between taking deferiprone and the development of cardiac failure in this case may contribute to an understanding of the possible cause of cardiac disease. The patient was on deferiprone for only 6 weeks and developed severe arthralgia which led to the discontinuation of deferiprone. He reported no cardiac manifestations during therapy with deferiprone and in spite of 22 months of treatment with desferrioxamine prior to its discontinuation due to vestibular toxicity, his serum ferritin values were still reported to be 1950 μg/L. It is not unreasonable to assume that cardiac loading of iron had continued while receiving deferoxamine. Dyspnea was not reported until a period when there was no chelation therapy being administered, although the authors refer to the time period as "a few days after discontinuation of deferiprone". This was followed by cardiac failure 2 weeks later, again presumably during a period with no chelation therapy. The basis of the authors’ considering that deferiprone may have been responsible for the cardiac failure is unclear. In a patient with chronic iron overload and ferritin and liver iron concentrations in the ranges reported, it is unreasonable to assume that a very short period of therapy with deferiprone could be sufficient to remove enough cardiac iron to bring him into a non-risk zone. On the other hand, if deferiprone had been keeping the patient’s pending cardiomyopathy at bay, weeks without chelation therapy could very well have tipped the scales in favour of iron-induced heart disease.

The authors acknowledge that the patient underwent a bone marrow transplant approximately 1 month after discontinuation of deferiprone despite cardiac failure, and died shortly thereafter. It is well documented that in the absence of intensive iron chelation therapy, death usually occurs within 6 months of the onset of iron-induced cardiac failure. There is no mention of any iron chelation therapy being provided to the patient once deferiprone was discontinued, which could very easily have set him up for this iron-induced cardiac event.

In our clinic, the only cardiac related deaths in patients being treated with deferiprone either alone or combination with desferrioxamine that we have seen, were in two patients with very high serum ferritins levels (mean 5 years ferritin prior to death 6844 and 9761 μg/L). These two patients were poorly compliant to chelation therapy. Other than this, in general, we have seen a reversal of cardiac dysfunction in patients who receive combination deferiprone and desferrioxamine therapy and also a significant reduction in cardiac iron loading as assessed by MRI in patients who were at significant risk of developing cardiac failure because of cardiac iron levels.

We agree with Aqodad et al. that careful cardiac monitoring should be instituted for all patients at risk of iron-induced cardiac disease. The monitoring should be conducted by cardiac T2* with a reliable and validated magnetic resonance imaging technique for assessing myocardial iron levels, thereby providing a means to measure the risk factor of developing iron-induced cardiac disease [4].

In summary, the evidence presented illustrates a patient with long standing severe transfusional iron overload, who, after having failed to be controlled on deferoxamine was
switched for a short period of time to deferiprone, and then deferiprone was discontinued. While apparently not on any chelation therapy, the patient developed a cardiomyopathy and then, while still not on any chelation therapy, progressed to heart failure. Despite his poor cardiac status, he underwent a bone marrow transplant and the patient died in heart failure. The authors speculate that the event might have been induced by deferiprone. While it is not possible to categorically exclude deferiprone, at least in the differential, the evidence seems to strongly suggest that iron-induced cardiomyopathy, precipitated by a period without chelation therapy and bone marrow transplantation were the cause. We are concerned that the authors’ assessment of causality was inadequately documented and that their opinion might compromise treatment of patients with iron-induced cardiac dysfunction despite the published evidence of the benefits of deferiprone alone or in combination with deferoxamine in reversing cardiac dysfunction [5]. Indeed there are at least three reports on the complete reversal of cardiomyopathy in patients previously on deferoxamine alone with intensive combination therapy with deferoxamine and deferiprone [6—8]. There are also some promising reports that deferasirox may reduce cardiac iron and may help prevent death from cardiac failure although its efficacy in reversing cardiac dysfunction must be demonstrated on the long term [9].

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References


Fatal congestive heart failure with deferiprone: Answer to letter from Ladis et al.

We would like to thank Dr Ladis and his colleagues for their interesting comments about our recently published case report.

We fully agree with their comments about underlying cardiac iron overload, which may have been the cause of preexistent asymptomatic cardiac disease. Although we did not perform cardiac magnetic resonance imaging, this was highly probable, due to the amount of iron transfused [1]. It is also clear that the bone marrow transplant was an aggravating factor and played a major role in the fatal outcome in this patient.

The key point is that 15 days following the administration of a 6 week course of deferiprone dramatic cardiac failure occurred. We searched for a factor explaining this sudden failure (the patient had been completely asymptomatic until then) but could not find one. It should be noted that the cardiac decompensation was preceded by severe arthralgia. Also, this event was strikingly similar to the features reported after vitamin C treatment in highly overloaded hemochromatosis and attributed to redistribution of iron with release of non transferrin bound iron which is a toxic form of iron [2]. Therefore, the hypothesis that deferiprone might have been responsible for a rise in NTBI seems logical, which could play a role both in the arthro-