Treatment of cardiac iron overload in thalassemia major

The inexorable tissue iron accumulation in thalassemia major is well documented and is fatal unless chelation therapy is given to remove the iron from the tissues. Desferal thus revolutionized the treatment of iron overload in thalassemia and dramatically improved survival. Desferal has been widely available now for over two decades and initially it was thought that life expectancy might be open-ended for the majority of patients, but this has not been achieved. Recent cohorts show that only 50% of patients currently survive beyond the age of 35 years, and with inadequate chelation, only 30% of patients survive over the age of 30. Some cohorts have, however, done better than this. By far the commonest cause of death is cardiac complications, accounting for well over half of all deaths. Intensive chelation therapy with defereroxamine can prevent cardiac complications, and may reverse the deleterious effects of severe iron overload. However, there are three main, unresolved problems that have emerged with the use of desferal monotherapy. First, it must be given as intravenous or subcutaneous infusions over prolonged periods, which are painful, cumbersome, and inconvenient and therefore compliance is compromised. An orally active chelator might offer significant advantages by improving compliance. The only current orally active chelating agent is deferiprone. Although desferal may be a more efficacious chelator, the issue of compliance may partly redress this balance. Second, the cost and difficulty of treatment would be significantly reduced, which is important considering the worldwide distribution of thalassemia. Third, and most importantly, there is still significant cardiac mortality with desferal, which might be lower with a different therapy. On this third issue there have been recent changes in our understanding of the distribution of iron throughout the body, and how this is affected by chelation. This is changing the understanding of iron distribution and its management.

In the assessment of tissue iron loading, until recently, the main methods of assessing iron loading were serum ferritin and liver iron concentration. It is well recognized that serum ferritin is affected by a whole host of different factors, and is an unreliable marker. Liver biopsy has until recently been regarded as the gold standard to assess total body iron, and hence the risk of not only hepatic complications but also cardiac complications, accounting for well over half of all deaths. Intensive chelation therapy with defereroxamine can prevent cardiac complications, and may reverse the deleterious effects of severe iron overload. However, there are three main, unresolved problems that have emerged with the use of desferal monotherapy. First, it must be given as intravenous or subcutaneous infusions over prolonged periods, which are painful, cumbersome, and inconvenient and therefore compliance is compromised. An orally active chelator might offer significant advantages by improving compliance. The only current orally active chelating agent is deferiprone. Although desferal may be a more efficacious chelator, the issue of compliance may partly redress this balance. Second, the cost and difficulty of treatment would be significantly reduced, which is important considering the worldwide distribution of thalassemia. Third, and most importantly, there is still significant cardiac mortality with desferal, which might be lower with a different therapy. On this third issue there have been recent changes in our understanding of the distribution of iron throughout the body, and how this is affected by chelation. This is changing the understanding of iron distribution and its management.

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The myocardial T2* technique has provided at least part of the answer to the high cardiac mortality. There is a lack of concordance between iron levels in different tissues (especially heart and liver), suggesting that reliance on single tissue iron loading to determine appropriate chelation is unsound. In addition, patients on long-term deferiprone have significantly less myocardial iron loading with an associated increased ejection fraction than those on long-term desferal. This suggests that deferiprone has a cardioprotective effect.

In this issue of Haematologica, Piga et al. compare the frequency of cardiac complications in patients managed with desferal and deferiprone. Each patient was on their respective treatment for a period of at least four years. They were then assessed for occurrence or worsening of cardiac complications over the follow-up period. The assessments included both physical cardiologic parameters, such as NYHA class and physical examination findings, but also diagnostic parameters such as ECG and echo-Doppler changes. Prior to the treatment all patients were treated with desferal. Compliance was also assessed during the study period. The authors found that there was significantly less cardiac disease in the deferiprone-treated group than in the desferal-treated group. It is perhaps also worth noting that the 2 patients with the worst NYHA class were both on desferal, and that none of the deferiprone-treated patients died during the study period, whereas 3 patients in the desferal arm died of worsening cardiac disease. These findings add further credence to the suggestion that deferiprone has a cardioprotective effect over desferal. As discussed by the authors, this may be explained by the physical characteristics of deferiprone. Deferiprone can cross cell membranes, and may therefore be more effective at removing intracellular iron pools. Interest-
ingly, although lack of desferal compliance has been thought to account partly for the apparent cardioprotective effect of deferiprone, compliance was 85% in the desferal-treated group and only 4% higher in the deferiprone-treated group. With this level of desferal compliance, this is unlikely to be an adequate explanation for any differences in outcomes. The importance of an orally acting agent that is cardioprotective cannot be underestimated. Further prospective and randomized studies are now needed to confirm these initial findings. Further work should also use myocardial iron measurements, and T2* is ideally suited for this.

This now raises the possibility of tailor-made chelation strategies based on differential tissue iron distributions in different patients, where desferal is better for liver iron chelation, and deferiprone more effective in the heart. More aggressive liver iron chelation may be needed in patients who are hepatitis C positive,17 and some patients may require a combination of agents.

The use of tailor made chelation regimes and combining the 2 agents in lower doses, may both alleviate side effects, and reduce mortality and morbidity further. It is known that iron removal increases if desferal and deferiprone are used in combination. With the possibility of further chelating agents in the near future, treatment may soon be on a cocktail of chelating agents, tailored to an individual patient’s needs, and based on a sound understanding of their respective tissue iron distribution.

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References


Rituximab: a new therapeutic tool for primary immune thrombocytopenic purpura?

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenic purpura, is an acquired disease of children and adults defined as isolated thrombocytopenia. In pivotal experiments (which would be totally unfeasible today), Harrington and others demonstrated that infusion of whole blood or plasma from ITP patients into normal volunteers caused thrombocytopenia.1 Moreover, subsequent studies demonstrated the crucial role of the spleen in determining platelet loss from the circulation.2 These data strongly suggested that anti-platelet antibodies were responsible for the disease.

Many years of research have provided additional details on the nature of the antibodies involved (directed primarily against GPIIb/IIIa and/or GPIib/IX)3-5 but still little is understood about the primary mechanism which triggers autoantibody production and, more importantly, what is the basic pathogenetic mechanism of the disease. One wide-