

# Transfusion-dependent thalassaemia: a new era

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*With three iron chelating agents now available, management options have substantially increased*

Outcomes in patients with thalassaemia major have been revolutionised over the past 50 years. Without transfusions, death usually occurred in the first decade of life. In the 1950s, transfusions were given to manage the symptoms of anaemia, which resulted in increased survival but significant morbidity. In the 1960s, regular blood transfusions were introduced to maintain relatively high mean haemoglobin levels in order to suppress the production of abnormal red cells in the bone marrow. This permitted good quality of life in childhood, but led to cardiac death from transfusional iron overload at a mean age of 18 years.<sup>1</sup> Fortunately, the parenteral iron chelating agent desferrioxamine was also introduced in the 1960s, and its use to control iron load led to improved survival<sup>2</sup> and reduced morbidity.<sup>3</sup> Nevertheless, the difficult treatment regimen (subcutaneous infusion for 8–12 hours per night, 3–7 nights per week) resulted in poor compliance. Cardiomyopathy remains the most common cause of premature death in patients with thalassaemia,<sup>3</sup> even in well chelated patients.<sup>4</sup>

The recent development of new magnetic resonance imaging (MRI) techniques (T2\*) has allowed the assessment of tissue iron levels (albeit indirectly), including myocardial iron levels, and has increased our understanding of iron overload. The use of this methodology has demonstrated that practically all thalassaemia major patients with cardiomyopathy have excess cardiac iron. It has also shown that the conventional surrogate markers — liver iron concentration and/or ferritin levels — are not predictive of cardiac iron levels.<sup>5,6</sup> Cardiac iron overload has also been observed in patients who were previously thought to be well chelated.<sup>5,6</sup>

The licensing, in 1999, of the oral chelating agent deferiprone as a second-line iron chelator was initially embraced as a relief for patients who could not tolerate desferrioxamine or had adverse reactions to it. Recent data demonstrate that deferiprone is more effective than desferrioxamine in removing excess cardiac iron<sup>7</sup> and suggest that it may even be more protective of endocrine glands (eg, the pancreas, thyroid and gonads).<sup>8</sup> The beneficial effect may be related to the characteristics of deferiprone, which has a low molecular weight, an uncharged molecule and favourable lipophilicity and is largely unbound to plasma proteins, enabling easy entry into all tissues. The use of deferiprone and desferrioxamine in combination has even been demonstrated to reverse established cardiomyopathy.<sup>9</sup>

The bottom line is survival. For ethical reasons, prospective studies of survival are not feasible, and in any case it would take many years to acquire meaningful results. Data from observational and retrospective studies must therefore be given due consideration. An Italian epidemiological, natural history study of 516 patients demonstrated a higher incidence of cardiac disease and cardiac-related deaths in a group of patients who continued on desferrioxamine (359 patients) than in a group who were switched to deferiprone (157 patients).<sup>10</sup> The latter group experienced no de-novo cardiac disease or iron-related deaths. Reports from other centres are also indicating reduction in cardiac deaths over the past few years, which may be attributable to the use of deferiprone.<sup>11</sup>

Both chelators are needed because the value of desferrioxamine is limited by poor compliance with treatment, and, although deferiprone is well accepted, its use is limited by concerns about

potential adverse effects, particularly agranulocytosis. Although the incidence of this complication is low, its potential occurrence necessitates weekly blood counts. Some patients also complain of the relatively large number of tablets that need to be taken in three divided doses daily.

The article by Kidson-Gerber and colleagues in this issue of the *Journal* (page 72)<sup>12</sup> comes from a unit in which patients are offered optimal management with appropriate monitoring and treatment, including prescription of desferrioxamine and deferiprone. The authors quantified compliance by comparing prescriptions written with the actual amount of drug collected from the hospital pharmacy. This confirmed that, on average, patients took only 50% of the desferrioxamine prescribed, and only 10% took it exactly as prescribed. Their report firstly confirms the relationship between acceptance of chelation therapy and morbidity, making it clear that acceptance and use of chelation therapy is crucial for satisfactory outcomes, and secondly demonstrates increased compliance with oral chelation therapy. Seventeen patients (mainly non-compliant with desferrioxamine therapy) were additionally prescribed deferiprone. Relatively few took the prescribed quantity of desferrioxamine, but most took the deferiprone, sometimes even more than prescribed, indicating “creep” on the part of the patients towards the more acceptable oral therapy.

The therapeutic armamentarium has been further expanded by the recent licensing of the oral chelator deferasirox in Australia and a number of other countries. Deferasirox is a soluble tablet that needs to be taken only once daily and therefore has high patient acceptance. At adequate doses, deferasirox is equivalent to desferrioxamine in its ability to reduce liver iron concentration.<sup>13</sup> It has produced some adverse effects, particularly a rise in creatinine levels, but overall its safety profile is acceptable. Prospective studies of its ability to remove cardiac iron are in progress.

We need to ensure that all patients with thalassaemia major have access to MRI (to assess their myocardial iron load) and the full portfolio of iron chelation options. In developing countries, the treatments available will be strongly influenced by cost. If the newer oral agents can be shown to be at least as effective as desferrioxamine in preventing iron-induced morbidity, the higher cost of deferasirox may be offset by the reduced cost of managing complications secondary to poor tolerance of desferrioxamine treatment. With three chelating agents now available, the options for chelation management are significantly increased. Chelation therapy can now be tailored to individual patients based on the severity and tissue distribution of the patient's iron load. Intensive chelation regimens, combining deferiprone and desferrioxamine, are now possible, and data on the various potential combinations of the three chelators are expected to be available in the near future.

In summary, the management of thalassaemia major has improved significantly with the ability to monitor not only iron load but also the sites of iron loading, and because clinicians now have the choice of three iron chelators. It can be anticipated that mortality and morbidity will be further reduced and that life expectancy will approach the norm — especially for younger

patients. However, as shown by Kidson-Gerber and colleagues,<sup>12</sup> prognosis will be largely dependent on compliance with iron chelation therapy.

### Competing interests

Vasili Berdoukas is a consultant for ApoPharma, the company that markets deferiprone, and he has a confidentiality agreement with Novartis for the development of deferasirox. He has also received travel assistance and honoraria for attending conferences and for presentations at such conferences.

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