

Effective new treatments of iron overload in thalassaemia using the ICOC combination therapy protocol of deferiprone (L1) and deferoxamine and of new chelating drugs

An expert group of the International Committee on Oral Chelators (ICOC) has recommended a universally effective chelation combination protocol of oral deferiprone (L1) during the day (80-110 mg/kg/day) and subcutaneous deferoxamine (40-60 mg/kg) of a minimum of three nights per week for the rapid, safe and effective depletion of excess body iron in transfused iron loaded patients. Following the clearance of excess cardiac and liver iron load, deferiprone (L1) monotherapy at doses exceeding 80 mg/kg/day has been recommended for preventing the re-accumulation of excess iron in the heart and other organs. New chelators such as deferasirox may also be used in combinations with deferiprone (L1) and deferoxamine, especially in patients not tolerating the deferiprone (L1) / deferoxamine combination.

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There are very encouraging developments in the treatment of iron overload following the introduction of deferiprone (L1) in combination with deferoxamine, which appear to increase the prospects of universally effective chelation therapy for thalassaemia and other transfused iron loaded patients.¹ These prospects are also increasing following the conditional approval for clinical use of deferasirox (Exjade) in the USA in November 2005. Although some thalassaemia patients have reached 50 years of age, the mean age is much lower (eg 35 years in the UK) mainly because of ineffective deferoxamine therapy leading to iron overload and death primarily from congestive cardiac failure.^{2,3}

Variable doses of deferiprone (L1) (50-120 mg/kg) and deferoxamine (20-60 mg/kg) have been used in the past to achieve low, safe body iron levels. However, the effect of these treatments is variable and many patients still fail to reach low non-symptomatic body iron levels mainly due to non-compliance especially with deferoxamine, idiopathic low metabolic response, dietary factors, use of ineffective doses and drug-related toxicities.^{1,4,5}

The introduction of the deferiprone and deferoxamine combination therapy was originally suggested in 1992 to overcome the problems associated with monotherapies.⁴ A number of therapeutic protocols involving the combination have since then been developed for achieving optimum iron chelation therapy, including that of Origa et al recently.^{1,4,9} Some of these combination protocols have been presented and discussed during the 13th International Conference on Oral Chelators (ICOC) for the treatment of thalassaemia and other diseases in 2003.⁷ In several studies involving more than 100 patients it was shown that in more than 80% of the cases optimum therapy could be achieved in all categories of iron-loaded patients by using daily deferiprone at 75-100 mg/kg supplemented with administration of sc or iv deferoxamine 2-6 nights per week at 20-60 mg/kg.⁷ Serum ferritin and cardiac iron load as assessed by MRI T2* have been reduced and approached near physiological levels within 1-2 years of treatment. Cardiac function was improved with significant elevation of the LVEF and reduction of arrhythmias over the same period as also shown by Origa et al.⁶

The overall high dose, sequential and almost continuous 24-hour administration of the two chelating drugs appears to be highly effective in progressively reducing iron deposited in the heart and other organs.^{1,3,4} The mechanism also involves the elimination of the non-transferrin bound iron in plasma and iron from transferrin, both of which are implicated in the excessive iron loading of organs such as the heart.^{1,4,5}

An expert group of the ICOC committee (GJ Kontoghiorghes, A Kolnagou, JJM Marx, A Maggio and RW Grady) have recommended the ICOC combination protocol, which involves the use of deferiprone during the day (80-110 mg/kg/day) and deferoxamine (40-60 mg/kg) of a minimum of three nights per week for rapid, safe and effective depletion of excess body iron.^{1,7} Following the depletion of excess cardiac and liver iron load deferiprone monotherapy at doses exceeding 80 mg/kg/day has also been suggested for preventing the re-accumulation of excess iron in the heart and other organs.^{1,7}

No major or unexpected toxicity has been reported in the more than 100 patients that received the higher dose combination therapy compared to those receiving monotherapy with either drug.⁷ Compliance has also been substantially improved compared to that of deferoxamine treated patients. The overall efficacy of the ICOC combination is considered equivalent to that of iv deferoxamine, delivered via a port-a-cath, without the associated potential complications. Multicentre studies of the deferiprone and deferoxamine ICOC combination protocol are currently in progress assessing both the efficacy and toxicity aspects of the therapy.

In the meantime, more transfusional iron loaded patients having adverse effects or not responding to either deferoxamine or deferiprone monotherapies may benefit from deferasirox, which although may be ineffective as a monotherapy, it may be used in combination with deferiprone or deferoxamine.¹ The iron removal and toxicity profile of the new combinations are expected to be different from those of deferiprone and deferoxamine because of differences in the pharmacokinetic and ferromagnetic properties of deferasirox.^{1,5,10} Several other chelating drugs are also under development, which if approved the choice for treating patients will increase not only for use as a monotherapy but in combination therapies, which may overall be more effective and less toxic for different groups of patients not responding to one specific chelation therapy.¹

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