Combined use of oral chelators and desferrioxamine in thalassemia

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The standard iron chelation therapy is based on the use of deferoxamine (DFO) [1]. A subcutaneous infusion of 20–50 mg/kg/day over 8–12 hours 6–7 days a week promotes a total iron excretion of 0.15–0.5 mg/kg/day [2]. This may counterbalance the mean iron input from standard transfusional regimens of 0.25–0.5 mg/kg/day [3]. The effectiveness of this treatment is mainly determined by the compliance, that may vary significantly [4]. During these last few years the oral chelator deferiprone (DFP) has been approved in many countries and gained room at least as a second line option for patients where DFO is not tolerated or inadequate [5,6]. The relative lower efficacy is partially counterbalanced by the advantages in compliance due to the administration route. Recent results from independent studies suggest that deferiprone may be more cardio protective than deferoxamine. Patients on long-term treatment with deferiprone have a better myocardial MRI pattern [7], and less chance to develop a new cardiac disease or to worsen an existing one [8].

Rationale

The efficacy and tolerability profiles of DFO and DFP are very different, due mostly to the different physiochemical and pharmacological properties: molecular weight, Fe:chelator molar ratio, Fe affinity, Fe binding stability, and excretion. Some in vitro data suggested the possibility of an additive effect of combining the two chelators. A recent study from Link showed that the combination of DFO and DFP improved significantly the iron depletion rate from rat heart cells [9]. Clinical data are scarce. Grady performed the first exhaustive study on iron balance in thalassemia, assessing in each patient the fecal and urinary iron excretion with each chelator and finally in combination. The preliminary results show that in most patients an additive effect may be reached combining the two chelators. In some subject a synergistic effect has been observed. A “shuttle” hypothesis has been formulated to explain the described synergistic effect: DFP, crossing cell membranes more easily, could bind excess intracellular iron and mobilize into plasma, where DFO, with its higher affinity, may take it and speed up its excretion.

Clinical studies

Several studies have been published or presented at meetings on long-term use of the two drugs [10–18]. Unfortunately none of these is a randomized controlled trial and most do not satisfy high quality standards, nor the safety has been investigated systematically. Furthermore many different treatment schemes have been used, making difficult to summarize findings. Anyway the results seem to indicate a higher efficacy of combination therapy, in terms of urinary iron excretion, lowering serum ferritin levels, trend to normalize in iron-related MRI abnormalities both in the liver and in the heart, and in systolic function parameters. These observations, as the hypothesis that deferiprone could be faster or more efficient in removing excess iron from the heart have raised a lot of attention from clinicians, but should be verified with formal controlled studies.

Definition

A problem of terminology exists: in papers and presentations sometimes the prescription and dose timing is not fully described and under the umbrella ‘combination’ are associated very different treatments such as the daily taking of both drugs at full doses and simultaneously, or alternating the two drugs in some
way during the week. An approach to a common terminology could be the following:

- **Mono-therapy**: a single chelator is prescribed and taken for more than three months
- **Alternate therapy**: in a single day a single chelator is taken; the two chelators take turn on a weekly, monthly or quarterly basis (e.g., DFP five days a week and DFO two days a week)
- **Combination therapy**: prescription of more than one chelator, to be taken in the same day at least for a significant part of the period
  - **Sequential**: in a single day two chelators are taken in sequence; no substantial overlapping of the two drugs in the plasma (e.g., DFP thrice a day and DFO night time)
  - **Simultaneous or concomitant**: in a single day two chelators are taken at the same time; substantial overlapping of the two drugs in the plasma (e.g., DFO infusion starts at 7 PM and ends at 7 AM; DFP taken at 8PM, 11 PM and 7 AM).

Some other forms of combination exist, as a course of intravenous DFO at each transfusion to reinforce the iron chelation done at home.

**Potential applications**

Combination treatment should be potentially considered every time there is a need to search for an additive or synergistic effect. This include the reversal of severe iron-related complications, the most important of which is heart disease. At a new onset of heart disease it is important to provide a full protection from cardio-toxicity with a continuous treatment, to minimize the presence of non-transferrin bound iron in the plasma. Intensive DFO chelation with continuous intravenous infusion has been demonstrated to be effective. The addition of deferiprone seems to enhance the efficacy and to reduce the duration of intensive treatment.

Also for the prevention of iron-related complications may be an important field of application. The recent development of MRI techniques to quantify the heart iron and the relationship of MRI signal to systolic function give the rationale for a more effective prevention of this complication.

Another indication may be the achievement of safe tissue levels, in any patient where the iron overload is severe or in special conditions, such as the preparation to pregnancy or to a stem cell transplant or to antiviral treatment for hepatitis.

Another potential application regards patients with dose-related side effects to DFO or DFP. Individually tailored combination of the two drugs may minimize side effects, maintaining efficacy.

**Side effects**

This page is still to be written, as the experience with combination treatment is relatively recent. From the published studies it does not come out a trend to increase of the known side effects of both drugs nor the evidence of new ones. A raised prevalence of agranulocytosis has not been confirmed.

**New iron chelators**

The development of new iron chelators may enhance greatly the possibilities of combination treatment. In particular ICL670, a new tridentate oral chelator has good chances to be approved in the near future, due to the positive results of extensive clinical studies [19,20]. Its pharmacokinetics and pharmacodynamics offer interesting perspectives of potential combination with DFO or DFP. Well designed randomized controlled trials may answer important questions, but the sponsorship of combination therapy trials from industry is unlikely.

**Conclusions**

For the clinical practice: there is growing evidence that DFO and DFP combination treatment is more effective than s.c. DFO or DFP alone and may give benefit in certain clinical conditions such as heart disease. Little is known as regards the safety.

For the research: the results of many observations are large randomized controlled trials on combination therapy compared to mono-therapy. Clinically relevant outcomes should be studied, as liver iron concentration on short-term and heart disease and survival on long-term.

**References**


