Combined therapy with deferiprone and desferrioxamine in thalassemia major

Dimitrios Loukopoulos
Center for Clinical Research; Hematology Laboratory, Foundation of Biomedical Research of the Academy of Athens, Athens, Greece. E-mail: dloukop@bioacademy.gr

Iron accumulation resulting both through repeated transfusions and increased gastrointestinal absorption in patients with thalassemia major may cause serious organ damage and ultimately early death. Effective removal of this excess iron can improve both life quality and survival of these patients.[1] However, despite the wide recognition of these facts and the intensive research being carried out in the field of iron chelation, the latter is still not optimal since neither its efficacy and safety, nor patients' tolerance and compliance are yet satisfactory. Within this context and taking in consideration the relative paucity of iron chelating agents it is not surprising that clinical scientists put a great effort towards exploiting any potentially useful properties of the available drugs in order to extract the maximum possible benefit with the least possible harm.

The history of iron chelation starts some 35 years ago, with the introduction of desferrioxamine (DFO), a molecule extracted from cultures of Streptomyces pilosus, which binds iron in the blood of iron-loaded patients and excretes it in their urine and bile. DFO has a strong and selective affinity for iron and does not appear to have any major side effects. However, DFO displays poor bioavailability when given orally and has a rapid plasma clearance; this profile means that the drug is efficient only when administered parenterally over several hours in order to keep a constant serum level, and therefore led to the now standard therapeutic approach, i.e., administration of DFO by slow infusion overnight (6-10 hours) using a special pump. Intensive long term chelation therapy with DFO proved beneficial for a large number of patients, as evidenced by the gradual decrease of their serum ferritin and liver iron, but also by the fewer complications and longer survival rates.[1] However, for many other patients, uninterrupted therapy with DFO for long periods of time was almost impossible because of the associated physical distress and inconvenience. These factors caused poor compliance with therapy along with the expected serious consequences. It was therefore obvious that an orally-administered compound was a pressing need.

The field remained relatively sterile for several years, the only promising compound being a small molecule synthesized in the UK, which also displayed a high and selective affinity for iron, could be administered orally, had a relatively slow clearance, and was excreted in the urine as an iron-bound metabolite. The drug was introduced in a series of clinical trials under the name of L1.[2] Unfortunately, a formal Phase III trial was not part of the clinical devevelopment of L1, and some investigators questioned the overall effectiveness of the compound. In addition, debate about the side effects created concerns regarding the safety of L1. The controversy continued until accumulating evidence finally convinced clinicians that L1, now known as deferiprone (DFP) was an effective iron chelator, which, although unable to achieve negative iron balance in all patients, was capable of lowering the ferritin levels and liver iron concentration in many iron loaded patients, was well tolerated and had relatively few side effects.[3] The idea of combining both drugs came up during a turbulent session on iron chelation at an ASH Conference and was rapidly implemented mainly by UK-based clinicians.[4] The prevailing argument in favor of the combination was that the two chelators together would lead to negative iron balance en nearly all patients without the need for daily parenteral infusions of DFO. Combination therapy also took advantage of the finding that L1 could remove iron from the heart more efficiently than DFO, while DFO was more effective than L1 in removing liver iron. It was even proposed that the effect could be synergistic because DFP, as a small water soluble molecule, might easily enter the parenchymal cells, bind and bring the excess iron to the cellular surface, while DFO, would bind the surface iron and excrete it in the urine.[5] The initial publication was soon followed by a large number of reports, all agreeing that combination of DFO and DFP could not only diminish the ferritin levels and liver iron content in iron-loaded thalassemic patients but possibly also maintain iron balance in regularly-transfused patients without increasing the frequency and severity of the expected side effects.

Under this prism, the report of Orriga *et al.* in this issue6 does not convey a new message; its value lies in that it confirms the efficacy of the DFO/DFP combination in a large number of patients followed in one Center, and gives detailed information regarding side effects and potential cardioprotection. Efficacy was evaluated in 64 patients who received the DFP/DFO combination over a minimum of 12 months (range 12-57 months). Using serum ferritin levels as an index of iron overload, the authors report a significant decrease from 5243±2345 to 3439±2446 ng/mL (ca. 35%). However, although precise comparisons in the field of thalassemia are almost impossible due to the heterogeneity of the patients, it is still not clear whether this significant decrease can be ascribed to the DFP/DFO combination since, in an earlier report, the ferritin decrease in a cohort of 151 patients treated with DFP alone over a three year period was not significantly different when the assessment was carried out on patients starting therapy with ferritin levels above 2000 ng/mL.[7] On the other hand, what cannot be denied is that the measurements of urinary iron excretion were twice as large with combined therapy in contrast to therapy with DFO or DFP alone. The effect of the combined treatment on the heart remains to be be considered. The Orriga study shows an undeniable improvement in the cardiac function of most patients on DFO/DFP therapy as evidenced by the significant increase of their left ventricular ejection fraction (from 54.7±8.7 at baseline to 59.6±5.1 for the whole group of patients, and 48.6±9.0 to 57.6±6.0 for the 20 patients who were receiving cardiac therapy). However, here again the value of com-

bined therapy cannot be formally considered as larger than that of therapy with DFP alone because a direct comparison has never been made, while there are already several reports which show that monotherapy with DFP results in both an improvement of the ventricular function as well as an increase of the T2* values in MRI, thereby implying a significant decrease of the cardiac iron overload.[8] Moreover, considering that patients chelated with DFP had better survival and fewer cardiac deaths in comparison to those treated with DFO, the question of whether combined treatment may further improve the results remains open.[9]

The detailed description of the side effects observed during the 201 patient/years is the strong point of the Orriga paper; again, despite some minor differences which cannot reflect anything but the patients' variance, the reported side effects are similar to those already published elsewhere.[10] Gastrointestinal symptoms (32% of the patients) resolved on continuing DFP administration in all patients, except one who had to discontinue therapy. Arthropathy occurred less frequently than in patients treated with DFP alone, possibly indicating a more effective removal of iron from the joints. On the contrary, the incidence of agranulocytosis was higher than that previously published with DFP alone, while the incidence of mild neutropenia was similar. In all cases, the situation resolved following discontinuation of DFP. Finally, what appears interesting is the rapid normalization of the ALT values in the group of HCV negative patients who were put in the trial with ALT levels varying from 50 to 150 U/l. Conversely, the effect of the combined therapy on the ALT values of HCV positive patients was minimal or nil. In conclusion, the information given in this issue regarding the optimization of iron chelation confirms that the combination of DFO and DFP is effective indeed and is not associated with additional side effects; whether this approach is significantly superior to monotherapy with DFP cannot be formally confirmed and requires comparative long term trials. However, the fact that the daily excretion of iron when the patients were receiving the combination was twice as much in comparison to the excretion obtained by monotherapy with either DFP or DFO is in favor of a potential additive effect and supports exploring the simultaneous use of lesser doses of the above agents in the hope that this will reduce their potential, dose-dependent side effects.

References

1. Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini D, Del Vecchio GC, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica 2004,89:1187-93.
2. Hider RC, Singh S, Porter JB, Huehns ER. The development of hydroxypyridin-4-ones as orally active iron chelators. Ann NY Acad Sci 1990;612:327-38.
3. Kontoghiorgis JG, Aldouri MA, Hoffbrand AV, Barr J, Wonke B, Kourouclaris T, et al. Effective chelation of iron in beta thalassemia with the oral chelator 1,2-dimethyl-hydroxypyrid-4-one. Br Med J 1987;295:1509-12.
4. Wonke B, Wright C, Hoffbrand AV. Combined therapy with deferiprone and desferrioxamine.Br J Haematol 1998;103:361-4.
5. Grady RW, Berdoukas VA, Rachmilewitz EA, Giardina PJ. Iron chelation therapy; a better approach. The 7th Intl. Conference on Thalassaemia and the Haemoglobinopathies. Bangkok, Thailand, 1999:[Abstract 0018].
6. Orriga R, Bina P, Agus A, Crobu G, Defraia E, Dessi C, et al. Combined therapy with deferiprone and desfoerrioxamine in thalassemia major. Haematologica 2005;90:1163-8.
7. Ceci A, Balardi P, Felisi M, Cappellini MD, Carnelli V, De Sanctis V, et al. The safety and effectiveness of deferiprone in a large scale, 3-year study in Italian patients. Br J Haematol 2002;118:330-6.
8. Anderson LJ, Wonke B, Prescott E, Holden S, Walker JM, Pennell DJ. Comparison of effects of oral deferiprone and subsutaneous desferrioxamine on myocardial iron concentrations and ventricular function in β-thalassaemia. The Lancet 2002; 360:516-20.
9. Piga A, Gaglioti C, Fogliacco E, Tricta F. Comparative effects of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. Haematologica 2003;88:489-96.
10. Cohen A, Galanello R, Piga A Safety and effectiveness of long term therapy with the oral iron chelator deferiprone. Blood 2003;102:1583-7.