Deferiprone or deferasirox for cardiac siderosis in beta-thalassemia major

We read with interest the article by Pepe *et al.*[1] wherein the authors retrospectively compared cardiac iron burden measured by T2* magnetic resonance imaging (MRI) in three groups of beta-thalassemia major patients treated with desferrioxamine, deferiprone, or deferasirox monotherapy for more than one year. The mean global heart T2* value was significantly higher in the deferiprone compared to the deferasirox group, allowing the authors to suggest that deferiprone has better efficacy in removing or preventing cardiac iron.

Recent evidence suggests that the low molecular weight oral iron chelator deferiprone and the newer oral agent deferasirox are particularly effective at removing or preventing cardiac iron overload.[2-5] Moreover, improved survival has been documented through several studies evaluating the role of deferiprone therapy in patients with beta-thalassemia major[6,7] and long-term results of deferasirox are anticipated. However, formal comparison between both drugs with regards to their efficacy in removing or preventing cardiac siderosis is limited, and studies in this direction are always welcome. Although Pepe *et al.*[1] are highly commended for attempting such a study, several concerns regarding data analysis and interpretation in their work limit the applicability of their conclusions. Although retrospective evaluation carries inherent limitations in methodology, essential attempts to improve the setting of comparison could still be made.

The authors found a statistically significant difference in the mean duration of active treatment between both drugs (deferasirox 2±1 years *vs.* deferiprone 4±4 years) before magnetic resonance imaging T2* measurement was undertaken. It is well-established that the kinetics of cardiac iron clearance are slow.[8] Moreover, data from the cardiac substudy of EPIC (Evaluation of Patients' Iron Chelation with Exjade) show that cardiac T2* continues to significantly improve with deferasirox therapy at yearly evaluations.[4,9] The imbalance in group size in the study of Pepe *et al.*[1] may not allow direct patient matching for duration of active chelator therapy; however, the authors could have categorized patients who received the drugs for similar intervals of time (e.g. over 1-2 years, over 2-3 years) and compared them at least as a secondary analysis. Although the authors did mention the discrepancy in duration of treatment amongst their limitations, the strong confounding effect (P=0.0001 at bivariate analysis) calls for the conclusions made to be re-examined. The same applies for the reported difference in mean left ventricular ejection fraction, liver iron concentration, and end-of-study serum ferritin level. The reported values for the latter seem particularly odd for deferasirox, as the mean serum ferritin level of patients did not change but even increased despite a report of excellent compliance. The authors did not provide any data on transfusion rate in either group during active treatment with chelators. The fact that both groups of patients had comparable pre-transfusion hemoglobin level does not necessarily mean they were assigned to similar transfusion regimens. Hence, the rate of transfusional iron loading during the period of interest may have been different and affected the observed outcome, especially if appropriate chelator dosing was not attained.

The aforementioned suggested analysis (comparing patients' cardiac T2* after a comparable duration of treatment) could only be meaningful if patients had similar baseline cardiac iron burden. The authors stated that there was no statistically significant difference in mean baseline serum ferritin level between deferiprone and deferasirox treated patients (mean value higher in the deferasirox group) and thus considered that both groups are comparable with regards to baseline iron burden. The relationship between cardiac T2* values and total body iron balance is quite complicated because the mechanisms and kinetics of cardiac iron uptake and clearance differ from other organs in the body such as the liver. Cardiac T2* does not correlate with serum ferritin concentration or liver iron concentration (especially utilizing hepatic T2* technique) in patients receiving chelation therapy in cross-sectional analysis, while longitudinal studies continue to imply a causal relationship.[10] Thus, current evidence does not permit the assumption that serum ferritin level predicts cardiac T2*. Hence, one cannot assume that baseline cardiac iron burden was similar in both groups without direct assessment using T2* magnetic resonance imaging. For optimal comparison, the 'difference' in cardiac T2* measurement (last available value minus baseline) after an appropriately defined and comparable period of time on each drug should be evaluated.

It is worthwhile noting that mean global heart T2* value was more than 20 msec and mean left ventricular ejection fraction was more than 55% in both deferiprone and deferasirox treated patients. Although cardiac T2* values below 20 msec correlated with cardiac dysfunction in several studies,[10] different values above this cut-off do not forecast a clinical picture. Moreover, the cardiac T2* values for deferasirox and deferiprone treated patients seem to overlap and confidence intervals are not reported. As such, we again stress the importance of observing a 'change' in cardiac T2* values before the efficacy of removing or preventing cardiac iron is confirmed.

Large prospective studies comparing the efficacy of deferiprone and deferasirox in removing and preventing cardiac siderosis are needed to establish the advantage of one drug over the other. Such studies are also expected to determine the optimal dosing, duration, safety, and cost-effectiveness of therapy and the added advantage of combination regimens of both drugs together or with desferrioxamine.

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