Transfusional Iron Chelation Inches Forward

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Editorial comment on the paper by Huihong Dou, Yuanhan Qin, Guoli Chen, Yanjun Zhao. Effectiveness and Safety of Deferasirox in Thalassemia with Iron Overload: A Meta-Analysis. Acta Haematol 2019;141:32–42

The care of thalassemia patients has resulted in a marked increase in life expectancy. As with other childhood diseases that have had improved life spans, new issues have arisen. In the case of thalassemia, an old issue has developed more urgency.

The mainstay of thalassemia treatment is transfusions [1]. Regular transfusions have created the first generation of children that often cannot be physically told from their unaffected siblings. However, with the regular transfusions inexorably comes transfusional iron overload. This iron burden all too often becomes the life-limiting toxicity of treatment. Damage to the liver, pancreatic islet cells, pituitary, and cardiac cells lead to many, if not most, of the cumulative end organ damage that limits both the quality of life and the life span.

The treatment for transfusional iron overload has also changed [2]. For over 40 years, deferoxamine (DFO) was the only effective iron chelation treatment available. In many ways, it remains the best chelator, except for how it is administered. This treatment, when tolerated, has been shown to improve survival. However, its parenteral route and its side effects were often too difficult for many patients to tolerate. The need for parenteral delivery was challenging for low resource areas that are home to most of the persons living with thalassemias. Even in the US, DFO or the critical pumps is sporadically not covered by insurance companies or simply unavailable. Many patients receive no or inadequate chelation. Over the last decades, oral formulations of bidentate and tridentate chelators have been developed in an effort both to increase effectiveness in lowering iron burden and to increase compliance.

In 2005, the FDA approved the first oral formulation of deferasirox (DFX), Exjade. Many centers quickly started using DFX as their first-line iron chelator. Despite the paucity of outcome data, the idea was that any formulation that can usually be tolerated is better than any formulation that often cannot be tolerated [3, 4]. Yet how well DFX compares to DFO has only been studied in a few well-controlled trials. Understanding how these medications may differ or even interact has become even more pressing as researchers are trying to combine the known differences in pharmacokinetics and pharmacodynamics among the 3 approved medications (DFO, deferiprone, and DFX). Some research suggests that such combinations can better target specific organ siderosis or better “shuttle” excess iron out of these organs [5]. Over time, however, side effects specific to these oral chelators have been emerging.

It is with this background that the meta-analysis by Dou et al. [6] begins to shed some insight into the real-world efficacy and side effects of DFO compared to one DFX formulation. Using a rigorous, Cochrane-style, systematic review and meta-analysis, the authors reviewed arguably the entire published literature at that time comparing DFO and DFX. The authors wished to compare mortality, serum ferritin levels, liver, and cardiac iron loading, and reported adverse events. Like many Cochrane reviews, this rigorous process began with 1,557 articles from 4 major medical databases. Applying strict criteria for unique, pertinent, randomized, controlled trials that reported the outcomes of interest, the authors were left with only 6 articles.

These 6 randomized, controlled trials enrolled a total of 1,102 patients on DFO compared to either DFX or placebo. The duration of the studies ranged from 2 to 52 weeks. The authors carefully evaluated each article for several types of biases, blinding, data completeness, and heterogeneity. This last being the property most often used to assess whether studies can be combined in a meta-analysis. After reporting on each study in detail, these researchers then combined these studies in a meta-analysis. In a series of descriptions and forest plots, the authors reported that although DFX is not superior to DFO, comparable iron chelation can only be achieved at the higher recommended doses of DFX (>30 mg/kg/day.) Only one of these studies addressed cardiac iron, finding DFX more efficacious than DFO. There was no difference in mortality between DFO and DFX. For side effects, few were serious. More alanine transaminase and creatinine increases, along with rashes and gastrointestinal issues, were noted in the DFX group. Although limited to 6 studies, this meta-analysis validates and supports results from many non-controlled or non-randomized studies.

Perhaps the most important finding is what was not found. Despite updated searches by the authors (last 6/2018), only 6 comparisons of short duration between DFO with the dispersion formulation of DFX (Exjade), not the pill formulation (Jadenu), met study criteria and were therefore available for comparison. Of note, these studies included transfusion-dependent and non-transfusion-dependent populations that may have different iron removal kinetics. This dearth of studies alone is worth reporting, as it emphasizes the need for future studies to include comparisons of all 3 approved iron chelators. This is especially true for studies with Jadenu, as this pill-coated formulation is often the first-line chelator in many centers [7]. Along with its increased use, more reports of side effects with Jadenu, especially the acquired Fanconi syndrome, increased creatinine, and elevated liver transaminases have emerged.

Several critical questions could not be well addressed in these studies. Can DFO or DFX lower iron to safe clinical levels in young patients for many years with acceptable side effects? Are there clinically important differences in side effects from intravenous versus oral administration of iron chelators? Can therapy targeted to the heart, pancreas, liver, or gonads succeed in reduce iron to safe clinical levels?

So where does this leave clinicians and researchers? First, for the clinician, many guidelines continue to recommend DFO as first-line chelation. Given the long clinical experience and the proven survival benefit, this makes sense. Indeed, many patients that have tolerated DFO prefer to stay with DFO, even when offered the chance to switch to an oral agent. Indeed, this current analysis shows that DFO is removing iron as effectively as DFX. However, many clinics have been using oral chelation first or in combination with DFO [2]. This analysis emphasizes that if Exjade is used, then the dose of DFX should be escalated to over 30 mg/kg/day. The clinician should be vigilant to monitor for liver, kidney, and gastrointestinal side effects. If these side effects appear and are not easily controlled, then likely the patient should be switched to DFO, or the dose of DFX reduced and DFO added. Second, for the researcher, the dearth of quality comparison studies, especially with the newer Jadenu, needs attention. High-quality, larger multicenter comparison studies between DFO and Jadenu are needed to guide not only monotherapy but also combination therapy as patients with thalassemia live longer. Such studies will guide clinicians in how to reduce their patients' life-long iron burden and its attendant end organ damage. There is great hope that this will improve not only their quantity, but also their quality of life.

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