Comment to: Development of lens opacities with peculiar characteristics in patients affected by thalassemia major on chelating treatment with deferasirox. Haematologica 2008;93:e9-10

Masera and colleagues recently published case reports of lens opacities in three patients with b-thalassemia major that were suggested to be associated with exposure to deferasirox (ICL670, Exjade®); the opacities developed 7, 16 and 26 months after initiating deferasirox therapy.[1] These three patients are from a total of 12 being followed by the authors at their institution. This reported incidence of new lens opacity development (25%) during deferasirox treatment is much greater than that observed in the overall population of patients who have received deferasirox in clinical trials, where ophthalmologic monitoring was performed at regular intervals. Of the 1034 patients in the five pivotal studies (whose mean treatment duration was 140 weeks with a cut-off date for follow-up of March 31, 2007) only sixteen (1.5%), including the three reported by Masera, experienced cataracts or lens opacities; most of these were considered by the respective investigator to be unrelated to deferasirox treatment.[2]

The authors do not explain or discuss the marked difference in incidence of lens opacities at their center when compared with the overall trial population. Deferasirox treatment was subsequently discontinued in all three patients described by Masera and treatment was switched to combined therapy with deferoxamine (DFO) and deferiprone. Patient #1 experienced new anterior opacities in the left and right eyes 22 and 36 months, respectively, after discontinuing deferasirox; while in patient #2 the initial opacity doubled 14 months after discontinuing deferasirox. If the original opacities were associated with deferasirox treatment the causes of these new opacities, which occurred many months after therapy was discontinued, are unclear and could equally be attributed to treatment with DFO and/or deferiprone. These data highlight the controversy surrounding the issue of lens opacities and chelation therapy, which is not adequately addressed in this article. The authors state that 11–14% of β-thalassemia major patients treated with DFO develop retinopathy and/or lens opacities.[3,4] However, these percentages are based on small patient numbers (53 and 29 patients, respectively). It is also worth noting that neither of the referenced studies suggest that the lens opacities were related directly to DFO 2 treatment.[3,4] Some studies have estimated that up to 50% of β-thalassemia patients have ocular abnormalities, including cataracts and acute visual loss, and that the frequency increases with age.[3–6]

Indeed, cataracts/lens opacities have been reported in β-thalassemia patients who had never received chelation therapy,[3–6] indicating that lens opacities may also be related to iron overload itself or to the underlying disease. One proposed mechanism to account for these findings is increased oxidation of lens protein by reactive iron radicals leading to protein precipitation.6 If the lens opacities are related to chelation therapy, the most widely accepted theory is that they result from over-chelation due to high chelator doses in patients with low serum ferritin levels. However, two of the three patients reported in this paper had high ferritin levels, suggesting that the observed lens opacities were not related to chelation therapy. The authors also mention that no ocular adverse events related to deferiprone treatment have been described; however, to ensure proper data interpretation it is important to know whether such adverse events have been systematically evaluated.

In summary, the authors conclude that the three new cases of lens opacities observed at their institution were associated with deferasirox treatment. However, both the current uncertainty surrounding the link between lens opacities and chelation therapy, and the substantially lower incidence rate of lens opacities observed in the overall population of deferasirox-treated patients, suggest that other factors may have also contributed. Ongoing experience with deferasirox from clinical trials and postmarketing use should hopefully shed further light on this issue.

Finally, it should be noted that there is an error in the second line of the publication. ather than *'…treated with deferasirox (DFO) develops…'* it should read *'…treated with deferoxamine (DFO) develops…'*

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