Development of lens opacities with peculiar characteristics in patients affected by thalassemia major on chelating treatment with deferasirox (ICL670) at the Pediatric Clinic in Monza, Italy

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Introduction

About the 11-14% of patients with thalassemia major (TM) treated with deferasirox (DFO) develops retinopathy and/or lens opacities with an unclear pathogenesis but with a clear age related pattern.[1,2] Possible causes can be either iron overload itself or DFO toxicity, with various mechanisms.[3,4] No ocular side effects related to L1 are described. During the core study referring to one year treatment with ICL670, cataract or lens opacities were reported as drug-related adverse events in 0.3% patients on ICL670 versus 1.4% patients on DFO.[5] We report the appearance of peculiar lens opacities in 3 out of 12 patients during treatment with ICL670.

Patients

Twelwe patients (6 M, 6 F) affected by TM, mean age 15 years (range 3.8-20.2 years) (median 20 years), followed by the Pediatric Department in Monza and routinely checked by the ophthalmologists of the Ophtalmology Clinic in Monza. These patients were treated from the first years of life with DFO at standard doses.

From September 2003, they were enrolled in the phase 3 study CICL670A0107: 6 were randomized to DFO which is to say they went on with DFO for one more year and then passed to ICL; 6 were randomised to ICL670 and started the new chelator straight on. For all patients the doses of ICL670 were defined and modulated according to protocol, considering single patient's iron overload parameters. According to the study protocol, periodic ophthalmic assessments were performed every 6-12 months, including: corrected visual acuity assessment, biomicroscopic evaluation of the lens with slit-lamp, tonometry, biomicroscopic fundus examination with non contact lens (90° lens). All the evaluations were performed by the same two ophthalmologists.

Case reports

During the CICL670A0107 study, three young patients (age 17, 16, 5 years) developed lens opacities at 7, 16, 26 months from the beginning of ICL670 therapy (Table 1). At the baseline examination time, two of them had no lens opacities while one patient (#1), with a past severe iron overload, had a small single spot-like opacity in one eye. No patients were nor had been on treatment with drugs known as responsible for lens opacities.

Lens opacities were monolateral cortical, linear and arranged in a radial shape in case #1 and #2, while in case #3 a bilateral diffuse subcapsular opacity was found. In patient #1 (right eye) the lens was also toric with a vacuolated aspect; this morphology disappeared one month after discontinuation of ICL670. None of the patients suffered from a visual acuity loss during the observation period, however all the three of them precautionally discontinued ICL670 and started a different chelating strategy (Table 1). Considering the unespected appearance and peculiarity of the opacities detected by slit lamp, the lens was then studied with Scheimpflug Camera (Anterior Eye Segment Analysis System EAS 1000, Nidek Ltd, Kamagori, Japan), which allows an

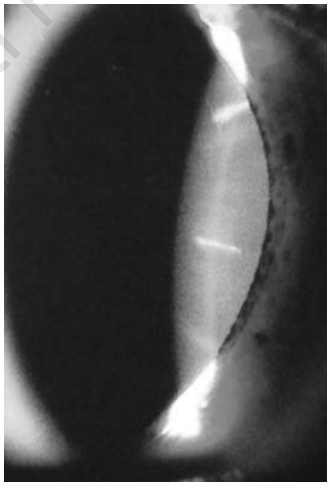

Figure 1. Morphology of lens opacities detected by slit lamp examination in patient n°1 after 7 months of ICL670 treatment: we see three linear opacities arranged in a radial shape. Similar lesions were detected in patient n°2.

Table 1. Characteristics of the 3 patients who developed lens opacities during ICL670 treatment.

Patient n./age (years)	*ICL670 dose (mg/kg/d)*	*Time of onset (months)*	*Baseline ferritin/LIC at the beginning of ICL670*	*Ferritin/LIC at stop ICL670*	*Therapy after ICL670 discontinuation*	*Lens opacities characteristics*
1 (17y)	30	+ 7	1930 / 16.4[A]	3700 / ND	Desferal+deferiprone°	linear radial cortical + swallen lens
2 (16y)	30	+ 16	1031 / 14.8 [A]	1079 / 6.5[B]	Desferal+deferiprone°	linear radial cortical
3 (5y)	20-40*	+ 26	1652 / 9.2[B]	2819 / ND	Desferal+deferiprone°	diffuse posterior subcapsular

**Dose increased according to Safety Board for progressive increase of ferritin values (20 mg/kg/die for 20 months, 30 mg/kg/die for 3 months, 40 mg/kg/die for 3 months); A= LIC (liver iron concentration =mg Fe/g liver dry weight) by biopsy; B= LIC (liver iron concentration =mg Fe/g liver dry weight) by SQUID; Ferritin = ng/mL; ND= not done; ° dose of Desferal 15-20 mg/kg/die; dose of Deferiprone 75 mg/kg/die.*

accurate analysis of lens opacities in terms of size and position.[3,6] Scheimpflug analysis confirmed all opacities detected by slit lamp.

In patient #1, 22 months after ICL interruption new radial cortical anterior opacities appeared in the left eye; after 36 months (February '07) in the same region where the previous linear opacities were detected (right eye), an anterior diffuse cortical opacity was observed by slit lamp examination. In patient #2, 14 months after ICL discontinuation (February 2007) the linear radial cortical opacity doubled, assuming a V shape. In patients #3 after 15 months follow-up (February 2007) the opacities were unchanged.

Conclusions

If we look back at our patients before the treatment with ICL670 was started, the overall prevalence of lens opacities was 17% (2/12 patients, after many years of DFO treatment) with homogeneous morphology and localization of lens abnormalities (intralental small round opacities), in analogy to what is reported in the literature.[2,3,7] The exposure to ICL670 was associated with the appearance of permanent lens opacities (see Figure 1) in 3 new cases at a mean distance of 16 months from initiation of ICL670 treatment. The morphology of the lesions was consistent with the pre-clinical findings in rats, in which lenticular changes, different from early cortical striations or vacuoles to mature cataract were found according to a time and dose dependent pattern, and attributed to an oxidative mechanism.[8] While the cluster of the three cases seen in our small cohort could be classified as a chance finding, it seems however more reasonable not to discard it as a signal, which requires a careful verification. A systematic well planned post marketing surveillance scheme for all new cases as well as for those who are switched to oral (either deferiprone or deferasirox) from parental chelation should be enforced by regulatory authorities, and/or adopted by the international scientific community who care for TM patients, to assure reliable prospective comparative information on the safety profile of the three chelating agents.

N. Masera, C. Rescaldani**, M. Azzolini MD**, C. Vimercati*, L. Tavecchia°, G. Masera*, V. De Molfetta,** and P. Arpa***

**Clinica Pediatrica, Università di Milano-Bicocca; **Divisione di Oculistica, Ospedale San Gerardo, Monza; °Centro Immunotrasfusionale, Ospedale San Gerardo, Monza, Italy*

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Correspondence: Nicoletta Masera, Pediatric Department, University of Milano-Bicocca, San Gerardo Hospital, via Pergolesi 33, 20052 Monza, Italy. Phone: +39.039.2333513. Fax: +39.039.2301646. E-mail: nicoletta.masera@pediatriamonza.it

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