AN OVERVIEW OF THE SAFETY OF DEFERIPRONE IN PAEDIATRIC PATIENTS WITH CONGENITAL HAEMOGLOBINOPATHIES AND CHRONIC IRON OVERLOAD

Adriana Ceci[1], Rosa Conte[1], Antonella Didio[1], Donato Bonifazi[2], Mariagrazia Felisi[3], Viviana Giannuzzi[1], Fedele Bonifazi[1]

[1]Fondazione per la Ricerca Farmacologica Gianni Benzi Onlus, Bari - Italy, [2]Consorzio per Valutazioni Biologiche e Farmacologiche, Bari - Italy, [3]Consorzio per Valutazioni Biologiche e Farmacologiche, Pavia - Italy

Introduction: Congenital Haemoglobinopathies (CHPs) represent the most severe forms of anaemia in Europe whose treatment include regular blood transfusions and chelation therapy. Currently, CHPs patients have different options of chelation therapy, as parenteral Desferrioxamine (DFO), oral Deferiprone (DFP) and Deferasirox (DFX), administered in monotherapy or in combination. None of the existing chelators have been sufficiently studied in all the paediatric populations, therefore the availability of chelators at any age remains a huge problem and a relevant therapeutic need. DFP was the first licensed oral iron chelator and is available worldwide. However, despite a wide experience on its use even in young people due to the early start of iron chelation therapy, published data on safety in children are insufficient. To summarise data on the clinical safety of DFP in children, a review has been conducted.

Material and methods: Search in Regulatory Assessment Reports (Food and Drug Administration 'FDA', European Medicines Agency 'EMA'), in clinical studies databases (clinicaltrial.gov, EUDRACT, EU PAS Register-ENCEEP) and in literature (Pubmed) was performed. The evaluation was conducted from 25/08/1999(FerriproxÒ Marketing authorisation data) to 30/06/2018. Studies including CHPs paediatric patients on DFP therapy (both monotherapy and combined therapy) were analysed. Only studies including well defined paediatric age' groups have been considered.

Results: The safety of DFP was evaluated in a total of 1232patients included both in studies sponsored by the Marketing Authorisation Holder and in independent research-driven studies. No paediatric detailed data have been retrieved from the three major sponsored studies on DFP included in the 1999FerriproxÒ Marketing Authorisation (MA) dossier, while a post-marketing paediatric study was included in 2010. Among of 71studies selected in our search, 21were reporting safety data and were included in the analysis. The studies that have been analysed were 12interventional and 9observational including a large safety observational study. 211patients were aged less than 6years (17.1%) and only 4(1.9%) were naïve at the time of the study. 839(68.1%) patients were in DFP monotherapy, 297(24.1%) in combined therapy with DFO and 96(7.8%) in combined therapy with DFX. Combined therapy was both sequential (16patients, 4.1%) and simultaneous (334patients, 85%). The most serious ADR related to DFP, agranulocytosis, has been reported with an incidence of 1% (0.7% in monotherapy and 1.5% in combined therapy), similar to what observed in adults. Elevated liver enzymes were the most frequently reported ADRs in monotherapy (26.1%), followed by arthropathy in 16.3% and neutropenia (9.8%). The ADRs most frequently reported in combined therapy were neutropenia (12.2%), followed by elevated liver enzymes (9.7%) and increase of creatinine blood level (8.1%, observed in patients in DFP+DFX). However, data on combined therapy was available only in a limited patients' group with contradicting results regarding in particular the safety of the sequential or simultaneous use. Several studies showed that this latter use is more frequently associated to agranulocytosis/neutropenia.

Discussion and conclusion: The DFP safety profile is in line with the latest information in the Summary of Product Characteristics (SmPC) and the available data in paediatrics demonstrate that DFP is generally safe also in young patients. The risk for agranulocytosis and for other relevant ADRs in children treated with DFP are not significantly different from other groups of age, but caution is recommended in very young children and in combined therapy if two chelators are administered simultaneously. Notwithstanding safety data are increasing, further research to better investigate genetic or other risk factor correlated to agranulocytosis and to recommend how to use safely DFP in combination, is necessary.