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LETTER

Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with nontransfusion-dependent thalassemia syndromes

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Dear editor

As the scientific steering committee for THALASSA (an assessment of Exjade in nontransfusion-dependent thalassemia [NTDT]), we read with interest the review by Kontoghiorghe and Kontoghiorghes entitled "Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with non-transfusion-dependent thalassemia syndromes" published in January 2016.[1] While this review provides a detailed overview of available iron chelators for the treatment of NTDT patients, there remain some factual inaccuracies and misrepresentations of data related to deferasirox. Therefore, we believe that the current article may be misleading to readers of *Drug Design, Development and Therapy*.

Foremost, there is no mention that to date deferasirox is the only oral iron chelator approved for the treatment of chronic iron overload in NTDT patients. Approval was granted following the successful THALASSA trial (n=166), the first randomized, controlled study showing that deferasirox significantly reduces iron overload in NTDT patients with a manageable safety profile.[2,3] As such, we feel that the recommendation by Kontoghiorghe and Kontoghiorghes for deferiprone as the first-line treatment of NTDT patients is concerning given the absence of robust clinical evidence and regulatory approval. Indeed, deferiprone is recommended as a second-line treatment in most clinical practice guidelines worldwide. Furthermore, the authors draw many of their conclusions regarding deferasirox tolerability from postmarketing surveillance information, yet neglect to mention premarketing clinical trial experience from ~700 adult/pediatric patients supporting a clinically manageable safety profile for deferasirox with appropriate patient monitoring.[4] Both sources of data should be considered for a balanced analysis of drug-related tolerability issues.

There are also several specific claims regarding deferasirox that we would like to highlight as inaccurate and provide further supportive evidence to the contrary:

- "DFX appears to increase iron and other toxic metal absorption." Concerns about the increased iron uptake were addressed during the development of deferasirox and were shown not to occur.[5] Given the structural similarities between iron–deferasirox and aluminum–deferasirox complexes,[6] increased gastrointestinal uptake of aluminum would not be anticipated in vivo. These data were neither discussed nor cited.

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- "[…] excess iron removal from the heart by DFX is not effective and in most cases very slow, with no improvement in LVEF, especially in heavily iron-loaded TM patients." Clinical evidence for deferasirox in the removal of cardiac iron has been demonstrated in the large, prospective EPIC cardiac substudy and the randomized CORDELIA study.[7,8] Deferasirox was effective in removing cardiac iron and maintaining cardiac function in thalassemia patients with mild, moderate, and severe cardiac siderosis. Furthermore, in CORDELIA, although the enrolled patients had left ventricular ejection fraction ≥56% at baseline, small improvements were noted in some patients.[8,9] This is important because even small improvements can reduce the risk of heart failure.[10]
- "The use of DFX is not recommended for iron-loaded patients with serum ferritin lower than 500 ng/mL." The authors cite deferasirox-labeling information from 2010, prior to updates in 2015 that include the indication of deferasirox for NTDT patients. In the 2015 version, treatment interruptions are indicated when serum ferritin is <300 ng/mL, the safety of which was established in THALASSA.[4,11]
- "Lower efficacy and higher toxicity was reported for DFX in TI […] by investigators not related or funded by the manufacturers of DFX." This statement is based on one retrospective, single-center study of a combined population of β-thalassemia major and intermedia patients.[12] The cited study by Karimi et al[13] was an independent study, and there are additional investigator-initiated studies[14,15] that were not cited. Together with the outcomes of THALASSA, results from these studies provide credible evidence supporting the efficacy and safety of deferasirox in NTDT patients.
- "DFX is also very expensive and cannot be afforded by the vast majority of patients." Here, there is no mention of cost-effectiveness analyses by Karnon et al[16] who have demonstrated that the higher drug cost of deferasirox may be offset by savings due to the cost of DFO administration (eg, pumps and needles) or the reduced need to treat iron overload-related complications that can develop when patients are not compliant with DFO.

Finally, we feel it necessary to inform readers that Dr Kontoghiorghes has a conflict of interest in deferiprone, which has not been declared. Dr Kontoghiorghes was a member of the team who first synthesized deferiprone and has subsequently been described as the discoverer (eg, http://www.pri.ac.cy/research.htm).

We hope this letter clarifies some of the misconceptions presented by Kontoghiorghe and Kontoghiorghes and will provide physicians with additional information for consideration when deciding upon the most appropriate treatment for their patients.

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Author's reply

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Dear editor

There are many murky areas and marketing, legal, ethical, and other conflicts in the pharmaceutical industry, some of which involve physicians and academics. These activities and related ethical issues affect the safety and treatment of millions of patients.[1–11] Irregular and sometimes illegal activities for new patented drugs carried out by pharmaceutical companies, such as secrecy agreements with academics/academic institutions, can lead to biased reporting of the results of clinical trials and cover ups or underreporting of toxic side effects, as well as doctor's bribes, irregularities in drug pricing, corruption of the drug regulatory authorities, influential medical journals and patient organizations, etc.[1–11] The commercial influence and drug marketing tactics by pharmaceutical companies in the case of deferasirox affect the safety and long-term survival of thousands of thalassemia and other categories of transfused patients.[11–14]

Misinformation on Exjade has recently reached the stage of criminal investigations and fines, eg, of US $60 million settlement of a civil fraud lawsuit for understating life-threatening toxicities and US $45 million for false claim allegations being submitted to federal health care programs.[15–17] Furthermore, one of the largest law suits ever faced by a pharmaceutical company of US $3.5 billion for damages and civil fines was filed against Novartis in 2015 by the FBI of the US government involving Exjade and Myfortic.[15–17]

Similarly, there are many misconceptions, inaccuracies, and omissions in the letter of Taher et al regarding the toxicity, efficacy, and cost of Exjade in comparison to deferiprone and deferoxamine. Most of these issues have been extensively discussed in the past and reflect the commercial interference of pharmaceutical companies in academia, health authorities, medical literature, etc, all of which aim for the increase in sales of drugs.[1–14,18–21]

Taher et al omit to mention that the cause of fatal renal, hepatic, bone marrow, and hemorrhagic cases, as well as many other serious toxic side effects, including warnings about aluminum coadministration with deferasirox, are included in the Exjade drug labels.[18–21] There are also misconceptions by Taher et al, since there is no difference in the use of chelating drug protocols for thalassemia major, intermedia, "non-transfusion-dependent thalassemia", and other similar categories of patients with equivalent levels of iron load. In this context, the recent approval for the use of Exjade in iron loaded non-transfusion-dependent thalassemia patients does not mean that these patients have not been receiving effective treatment in the past 50 years nor that these patients cannot be continuously and effectively treated using deferoxamine and deferiprone.[22,23] Furthermore, the long-term effective and safe use of deferoxamine and deferiprone in iron loaded non-transfusion-dependent thalassemia patients outweighs any biased clinical trial results in a small number of deferasirox-treated patients controlled by Novartis.[22,23]

Major inaccuracies in the comments of Taher et al include the rate of mortality of 11.7% reported by the European Medicines Agency for deferasirox, whereas for deferoxamine and deferiprone it is <0.1% in postmarketing surveillance including deaths in clinical trials.[12,21] Furthermore and most importantly, substantial and rapid reduction or complete removal of toxic iron deposits, as well as elevation of left ventricular ejection fraction is observed in deferiprone- or deferiprone/deferoxamine-treated thalassemia patients, whereas no such results are observed in deferasirox-treated patients, where such improvements are rare or even nonexistent.[24,25] The reduction or elimination of cardiac mortality since the introduction of deferiprone in thalassemia patients worldwide has increased the survival of thalassemia patients to near normal life span levels, whereas the introduction of deferasirox is likely to reverse this improvement.[13,26]

Taher et al continue to mislead the medical community by reporting findings from Novartis-funded and -controlled clinical trials with deferasirox in thalassemia, which do not appear to be confirmed in clinical practice or by independent investigators.[22,25,27] For example, only ~10% of thalassemia patients are using deferasirox in Cyprus, whereas the majority are using deferiprone either in combination with deferoxamine or as a monotherapy.[13,26]

The recent increase in the maximum dose of deferasirox from 30 mg/kg/d to 40 mg/kg/d and its suggested use in non-transfusion-dependent thalassemia patients with serum ferritin <300 ng/mL is a desperate attempt to improve the efficacy profile of deferasirox and its sales in comparison to deferiprone and deferoxamine. However, these changes may further increase the toxicity risks, especially since earlier animal studies and clinical reports have shown fatal or serious renal and other toxicities.

In addition, there are misleading comments by Taher et al on the cost of deferasirox, which for example does not include any prophylactic renal and other clinical and biochemical tests for its toxicity, in comparison to deferoxamine and deferiprone. The high cost of deferasirox appears to affect patient treatment and safety, as well as government health budgets and the tax payers in general.[11–14] In particular, the high retail price makes deferasirox unavailable in developing countries where the vast majority of thalassemia patients live.[11–14]

Taher et al are public employees receiving undisclosed payments from Novartis for the promotion of Exjade, which may be contrary to the public and patients' interests.[15–17] In contrast, in my case as the inventor of the generic drug deferiprone and other investigational new drugs, these inventions are all part of academic research, which is widely described in the medical and other literature with no commercial involvement or receipt of any related income. This information was also disclosed to the journal during the submission of the paper.[12]

The author reports no conflicts of interest in the published paper entitled "Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with non-transfusion-dependent thalassemia syndromes", wherefore a statement/disclosure was submitted to the journal *Drug Des Devel Ther* before publication, indicating that "I have made the following discoveries: deferiprone (L1) and maltol iron[28] and also other discoveries, eg, deferoxamine (DF) suppositories.[29] I have also designed the combination of L1/DF[30] and the ICOC protocol.[31] I have also originally suggested the use of L1 in Friedreich ataxia, Parkinson's, and Alzheimer's diseases.[32] None of this work was supported by pharmaceutical or other commercial companies". It should also be noted that the patent on the generic drug deferiprone expired over 10 years ago, and the author receives no income or consultancies or any other support by any commercial companies.

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