

# Renal safety under long-course deferasirox therapy in iron overloaded transfusion-dependent $\beta$ -thalassemia and other anemias

## To the Editor:

Renal adverse events (AE) and increases in serum creatinine (SCr) have been reported in patients with transfusional hemosiderosis treated with deferasirox. Since the core registration trials, various extension and long-term observational studies have been conducted in pediatric and adult populations. These studies have described the reversible, non-progressive nature of SCr increases and confirmed the overall acceptable renal safety profile of deferasirox.

Given the chronic nature of treatment, especially in children with congenital anemias, a longer follow-up was thought opportune to demonstrate the absence of late or cumulative effects of deferasirox in real treatment practice. Italian sites enrolled 34% of the patients across the registration studies, and many of these patients have since then been followed up by the same physicians. This allowed us to conduct a retrospective chart review of SCr values, other renal parameters, and renal AEs in patients on iron chelation therapy for up to 13 years.

To minimize selection bias, the study set out to enroll all patients who were treated with at least one dose of deferasirox during the registration trials and had at least one post-baseline assessment of SCr. All available charts had an equal chance of selection but the first SCr, urinary protein, and urinary creatinine values available at the same visit were collected quarterly.

Of the 282 patients analyzed, more than 90% were observed for at least seven years following the registration studies. At quarter 1, 65 patients (23%) were less than 18 years of age and 217 patients (76%) were 18 years or older.  $\beta$ -Thalassemia was by far the most common underlying disease ( $n = 264$ ), followed by myelodysplastic syndromes ( $n = 9$ ), sickle cell disease ( $n = 7$ ), and other anemias ( $n = 2$ ). As commonly occurs in real world practice, most patients were not treated with the same chelator since the registration studies but were exposed to various chelating agents including deferasirox.

Baseline and worst value of SCr recorded during the registration studies, as well as the quarterly trend over the retrospective period are shown in Figure 1. Mean baseline value was  $53.39 \pm 13.45$   $\mu\text{mol/L}$

(range 20.35–87.96  $\mu\text{mol/L}$ ), while the worst value was on average  $79.73 \pm 20.19$   $\mu\text{mol/L}$  (range 35.40–156.50  $\mu\text{mol/L}$ ). During the retrospective period, mean/median SCr values were slightly higher than baseline but lower than worst value, with a stable quarterly trend (around 60  $\mu\text{mol/L}$  in mean) until quarter 43, when the number of patients began to drop considerably and mean/median values started fluctuating.

A subgroup analysis assessed SCr in patients ( $n = 98$ ) treated with only deferasirox during the retrospective period. Mean value was  $50.05 \pm 13.69$   $\mu\text{mol/L}$  at baseline and stable throughout the retrospective period, with mean values between 60 and 65  $\mu\text{mol/L}$ , corresponding to a 15%–20% increase from baseline at most quarters.

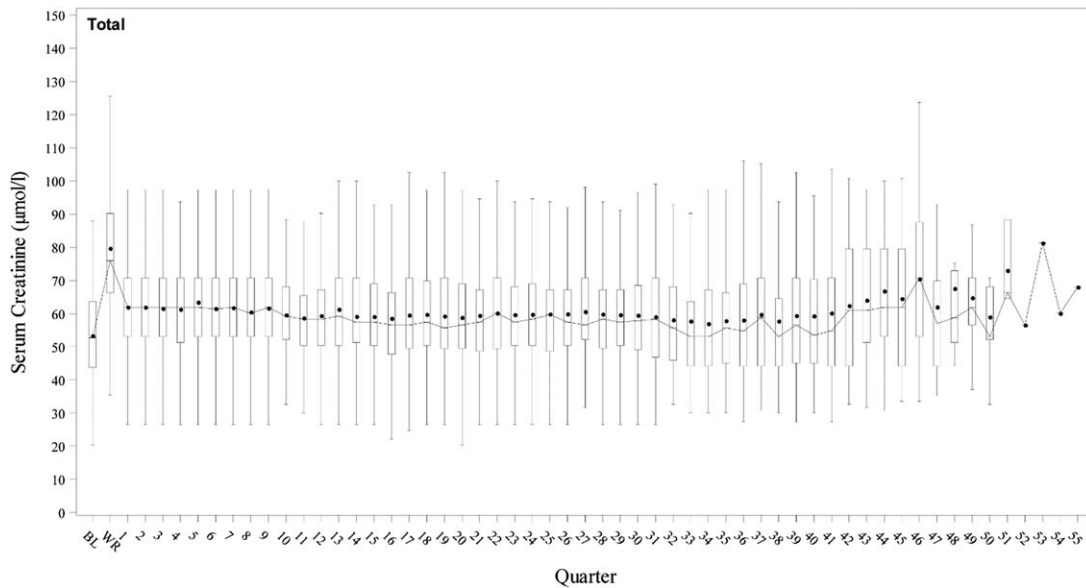
The SCr trend was traced in a subgroup made up of patients ( $n = 197$ ) with renal AEs or confirmed, notable renal laboratory values during the registration studies. Mean SCr at baseline was  $53.23 \pm 13.72$   $\mu\text{mol/L}$  (range 26.10–87.96  $\mu\text{mol/L}$ ), and mean worst value  $82.95 \pm 21.11$   $\mu\text{mol/L}$  (range 41.50–156.50  $\mu\text{mol/L}$ ). Mean/median values were then steady over time, higher than baseline but lower than worst value, and about the same as values for the full Safety Set (around 62  $\mu\text{mol/L}$  vs. 60  $\mu\text{mol/L}$ ), indicating that renal AEs occurring during the registration studies did not provoke irreversible or progressive long-term effects on renal function.

Although data for urinary protein, urinary creatinine, and creatinine clearance were often missing, these renal parameters also appeared to remain steady over the retrospective period, with values below the worst value reported in the registration studies.

During the retrospective period, renal AEs regardless of treatment relations were reported in 86/282 (30.5%) patients. The most common were nephrolithiasis (10.99% of patients) and renal colics (9.93%), followed by abnormal urine protein/creatinine (UPCR) ratio, abnormal/increased SCr, and proteinuria. At least one serious adverse event (SAE) was reported for eight patients (2.84%) (increased SCr, acute kidney injury, hematuria, hydronephrosis, renal colic, renal failure, and urethral stenosis). No causal relationship was suspected between the events and treatment with deferasirox.

Suspected deferasirox-related renal AEs were reported in 33 patients (11.70%). Proteinuria, abnormal/increased UPCR, and increased blood creatinine were the most frequently reported drug-related events. None of these events was serious but four were considered of severe intensity: increase of UPCR ( $n = 2$ ), proteinuria, and glycosuria. In most cases, deferasirox was temporarily interrupted or dosage was adjusted and no further action was required. Five (5) patients (1.77%) did however discontinue treatment permanently.

No cases of acute renal failure or of end stage renal disease were reported during the retrospective period. The one case of “acute kidney injury” mentioned previously as an SAE occurred during acute pancreatitis.



**FIGURE 1** SCr by visit (safety set). Baseline (BL) and worst (WR) values collected in registration studies, quarterly values in the retrospective period. The markers inside the boxes indicate mean values and the lines connect the median values over time. The length of the boxes represents the distance between Q1 (25th percentile) and Q3 (75th percentile). The whiskers represent the minimum values above  $1.5 \times$  IQR below Q1 and maximum values below  $1.5 \times$  IQR above Q3. IQR is the interquartile range, i.e. the distance between Q1 and Q3

Interpreting the data of our study may be difficult due to limitations such as the “retrospective” and “descriptive” nature of the study. The lack of data available for renal parameters such as UPCR and CrCl impedes a full evaluation of renal function but also highlights the importance of monitoring renal function as per label recommendations so that early renal function changes can be recognized.

The fact that many patients were treated with either multiple iron chelators or other iron chelators may have complicated the assessment of the specific effects of deferasirox on renal parameters. It however reflects what happens in real world clinical practice, and our study design, in agreement with suggestions from the EMA Committee for Medicinal Products for Human Use, included gathering data from patients not treated with deferasirox during the retrospective period to provide an analysis of renal consequences in the broader context of transfusion dependency, and not just in the setting of iron chelation.

In conclusion, these results in patients followed up for up to 13 years demonstrate the absence of profound nephrotoxic effects and the reversibility and non-progressive nature of treatment effect on renal function expressed through SCr. No substantial differences were observed between the adult and pediatric populations. The findings provide reassurances to physicians by contributing to accumulating evidence supporting the favorable long-term risk/benefit profile of deferasirox for the treatment of patients with transfusional iron overload.

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### AUTHOR CONTRIBUTIONS

Raffaella Origa, Antonio Piga, Immacolata Tartaglione, Giuseppina Della Corte and Gian Luca Forni on behalf of the Renal Chart Review Study Investigators served as investigators in this study. Andreas Bruederle and Chiara Castiglioni contributed to the study design, analysis, interpretation and reporting of the trial data. Jackie

Han served as the trial statistician and provided critical insights into Report and Analysis Preparation (RAP) development, the analyses and data interpretation based on the statistical testing carried out. All authors participated actively in interpreting the data and writing and critically reviewing this manuscript, approved the final manuscript content and controlled the decision to submit for publication.

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