bjh research paper

Deferasirox effect on renal haemodynamic parameters in patients with transfusion-dependent β thalassaemia

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Received 3 July 2014; accepted for publication 1 October 2014

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Summary

Some patients with β thalassaemia experience non-progressive creatinine increases with deferasirox, mostly within normal limits; the mechanisms involved are not fully elucidated. The effects of deferasirox on renal haemodynamics, including glomerular filtration rate (GFR) and renal plasma flow (RPF), were investigated in a Phase I, open-label study in β thalassaemia major patients with iron overload. Patients received deferasirox 30 mg/kg/d up to Week 8, followed by a 2-week washout period, and extended treatment up to Week 104 with a 4-week washout period. In the short-term study (n = 11), mean GFR and RPF declined from baseline to Week 8 (mean [%] change:−9·2 [−9·5%] and −105·7 ml/min [−17·8%], respectively). A similar pattern was observed during the long-term study (n = 5); mean GFR and RPF decreased up to Week 52 (−19·1 [−17·7%] and −155·6 ml/min [−26·1%]), with similar change at Week 104 (−18·4 [−17·2%] and −115·9 ml/min [−19·6%]). Measures returned to baseline values after each washout. Serum creatinine and creatinine clearance followed a similar pattern. Effects of deferasirox on renal haemodynamics were mild and reversible for up to 2 years of treatment, with no progressive worsening of renal function over time. www.clinicaltrials.gov: NCT00560820.

Keywords: iron chelation, deferasirox, glomerular filtration rate. thalassaemia, renal function.

Transfusion-dependent patients with β thalassaemia major now have longer life expectancies as a result of improved treatment outcomes (Borgna-Pignatti *et al*, 2004; Voskaridou *et al*, 2012). Complications that were previously less prominent, such as changes in renal function, which may increase in frequency as patients age or with increased transfusion duration, are becoming more apparent (Mohkam *et al*, 2008; Ponticelli *et al*, 2010; Bhandari & Galanello, 2012). While some studies suggest the influence of iron chelation therapy on renal haemodynamics (Economou *et al*, 2010; Hamed & ElMelegy, 2010), others implicate the inherent effects of the disease (i.e. chronic anaemia) and the consequences of transfusion-related iron overload (Koliakos *et al*, 2003; Sadeghi-Bojd *et al*, 2008). In a study of 91 non-diabetic patients with β thalassaemia and normal blood pressure, serum urea, creatinine and electrolytes, increased levels of urinary markers indicative of renal tubular dysfunction correlated positively with markers of iron overload but not chronic anaemia or chelation therapy (Koliakos *et al*, 2003). Collectively, evidence suggests that alterations in renal haemodynamics in patients with β thalassaemia are unlikely to be attributable to a single cause.

Given the lifelong dependence on transfusions, long-term chelation therapy will be required, hence a long-term manageable safety profile of chelators is a necessity. Deferasirox (Exjade®, Novartis Pharmaceuticals, 2013) has demonstrated significant short- and long-term efficacy in effectively reducing and preventing hepatic and cardiac iron burden in patients with thalassaemia and other chronic anaemias (Galanello *et al*, 2006; Cappellini *et al*, 2006, 2010, 2011; Vichinsky *et al*, 2007; Porter *et al*, 2008; Pennell *et al*, 2010, 2012; Vichinsky *et al*, 2011). The deferasirox clinical trial programme also highlighted that some patients experience dose-dependent serum creatinine increases >33% above baseline values. However, observed creatinine elevations in studies up to 5 years of duration were mostly within normal

First published online 17 November 2014
doi: 10.1111/bjh.13217

limits, non-progressive and reversible with dose reduction and/or interruption (Cappellini *et al*, 2006, 2010, 2011; Galanello *et al*, 2006; Vichinsky *et al*, 2007; Porter *et al*, 2008; Pennell *et al*, 2010, 2012; Vichinsky *et al*, 2011; Vichinsky *et al*, 2013).

The cause of these reversible creatinine increases has not been fully elucidated, but a likely mechanism of action appears to be the decrease in glomerular filtration rate (GFR) that occurs as a result of the pharmacological effect of deferasirox on the intra-glomerular haemodynamics of the kidney (Guo & Nzerue, 2002; Schetz *et al*, 2005). The underlying mechanism for the increase in creatinine might also be caused by an excess of drug relative to the amount of iron available for chelation. It is possible that, in the absence of sufficient chelatable excess iron, deferasirox removes enzymatic iron from one or more of the pathways that control glomerular filtration. Rapid iron removal may lead to a cascade of events following relative iron depletion (i.e. damage to mitochondria in renal tubular cells, activation of the tubuloglomerular feedback and vasoconstriction) that culminate in a reduction in GFR (Koren *et al*, 1991; Ponticelli *et al*, 2010; Musallam & Taher, 2012).

This Phase I, open-label study was therefore initiated to assess the effects of deferasirox on measures of renal function and markers of early kidney injury over the short and long term. The working hypothesis was that deferasirox produces a slight reduction in the GFR, an effect that is reversible following interruption of deferasirox treatment, thus indicating the absence of permanent nephron damage.

Methods

Patients

Eligible patients were aged at least 18 years, had a diagnosis of β thalassaemia major and were naïve to deferasirox treatment. Patients were required to be receiving regular transfusions at intervals of 2–5 weeks (iron intake ≥0·25 mg/kg/d) and to have been administered at least 20 units of packed red blood cells in their transfusion history. Iron overload was also required for study inclusion, assessed as serum ferritin levels ≥500 μg/l, or alternatively – if superconducting quantum interference device (SQUID) was the regional standard of care – using SQUID to measure liver iron concentration (LIC) ≥2 mg Fe/g dry weight (dw).

Key exclusion criteria included serum creatinine concentrations greater than the upper limit of normal (ULN), estimated creatinine clearance <60 ml/min [using the Cockcroft–Gault formula (Cockcroft & Gault, 1976)], urinary protein:creatinine ratio >0·5 mg/mg, or alanine aminotransferase exceeding 5 × ULN. History of nephrotic syndrome or treatment with drugs known to affect renal parameters also led to exclusion from the study. Patients provided written informed consent prior to entry.

Study design and treatment

This was an open-label, Phase I, single-arm study (NCT00560820) of deferasirox in patients with β thalassaemia and transfusional iron overload, which was conducted between 13 September 2007 and 24 April 2012 across three Italian centres. Study protocols were approved by the relevant ethics committees at each study site. The study was conducted according to the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The study and any amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each centre.

The original planned study duration of 8 weeks was extended to 108 weeks following a protocol amendment to enable the collection of longer-term data. Thus, the 108-week study comprised screening, initial treatment (8 weeks), extended treatment (94 weeks) and washout periods (2 weeks after Week 8 and 4 weeks after Week 104; Fig 1). During the first treatment period of 8 weeks, all patients received deferasirox 30 mg/kg/d, at least 30 min before a meal. Dose adjustments and interruptions were permitted after Week 10 for changes related to weight, serum ferritin or safety parameters. Regular medications required to treat concomitant conditions were allowed during the study.

Study objectives

The primary objective of this study was to estimate the effects of deferasirox on changes from baseline in GFR and renal plasma flow (RPF), as well as the corresponding filtration fraction (FF; ratio of glomerular filtration rate [GFR] to [RPF]), in deferasirox-naïve patients with regularly transfused β thalassaemia and transfusional iron overload.

Secondary objectives were to explore the relationship between change in serum creatinine and renal markers (GFR, RPF and FF), and the association between changes in serum ferritin levels and renal markers and serum creatinine. An additional exploratory objective was to evaluate the effects of deferasirox on urinary biomarkers.

Assessments

Changes from baseline in GFR and RPF were evaluated using plasma sampling and radiotracers [^{51}Cr-labelled ethylenediaminetetraacetic acid (^{51}Cr-EDTA) and ortho-^{123}iodohippurate (^{123}I-OIH), respectively] (Nakashima *et al*, 1996; Fleming *et al*, 2004). A trace dose of ^{123}I-OIH (37 kBq/kg) was administered intravenously into a forearm vein with an insulin syringe. After 44 min, a venous blood sample was drawn from the opposite arm of the ^{123}I-OIH administration. A trace dose of ^{51}Cr−EDTA (37 kBq/kg) was then administered with an insulin syringe. Venous blood samples were subsequently drawn at 120, 180 and 240 min after

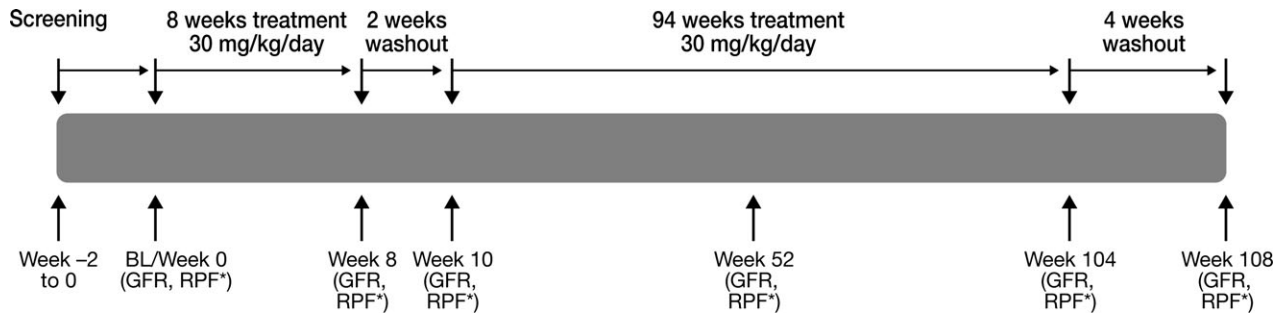

Fig 1. Study design. *GFR and RPF measured using ^{51}Cr-EDTA and ^{123}I-OIH. BL, baseline; ^{51}Cr-EDTA, ^{51}Cr-labelled ethylenediaminetetraacetic acid; GFR, glomerular filtration rate; ^{123}I-OIH, ortho-^{123}iodohippurate; RPF, renal plasma flow.

^{51}Cr-EDTA administration from the opposite arm to the infusion. The gamma-counter radioisotopic measurement from blood samples was performed on the same day of the test for ^{123}I-OIH and after at least 48 h for ^{51}Cr-EDTA. GFR and RPF assessments were performed at baseline and Weeks 2, 8, 10, 52, 104 and 108. The corresponding FF was calculated from the ratio of GFR to RPF.

Blood samples for measurement of serum creatinine were drawn at baseline, Weeks 1–4, 8 and 10, and monthly thereafter. Estimated creatinine clearance was calculated according to creatinine levels, age and body mass using the Cockcroft–Gault formula (Cockcroft & Gault, 1976). Serum ferritin levels were measured by blood sampling at screening, baseline, Weeks 2, 8 and 10, and monthly thereafter. LIC was measured by SQUID at baseline.

A panel of protein markers measured by Rules Based Medicine (RBM; Austin, TX, USA), called the Human KidneyMAP, was assessed in urine samples. Samples for biomarker analysis were collected at screening, baseline, Weeks 2, 4, 8 and 10, and monthly thereafter. RBM's Human Kidney MAP utilizes a multiplexed panel of biomarkers to detect early signs and locations of drug-induced kidney damage. The renal biomarkers included in this study were glutathione *S*-transferase-pi (GST-pi), microalbumin, neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1). In addition, the panel included measurement of urine creatinine, which was used for normalization.

Additional safety assessments comprised adverse event (AE) reporting (including serious AEs) and regular monitoring of haematology, blood chemistry, urine, vital signs, physical condition and body weight. Safety was assessed weekly up to Week 4 and fortnightly up to Week 10, then monthly thereafter.

Statistical methods

The planned enrollment was for 16 patients. However, challenges were experienced during enrollment; namely, the limited number of patients with β thalassaemia who were deferasirox-naïve and willing to undergo the demanding and invasive assessments of the study.

Analyses of renal measures and urinary biomarkers were performed in the full analysis set, which included all patients who passed screening and were enrolled in the study. The safety set comprised all patients who were enrolled and received at least one dose of deferasirox and who had at least one post-baseline measurement.

Results for mean change in renal haemodynamic and safety measures are presented descriptively. Absolute and percentage changes from baseline in GFR, RPF and FF were calculated using a linear mixed-effects model with visit as a fixed effect and patient as a random factor. The relationship between serum creatinine or serum ferritin and renal markers (GFR, RPF and FF) was tested using a linear or non-linear mixed-effects model with renal markers as dependent variables and change in serum ferritin or serum creatinine as fixed factors. Statistical software used was SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA). No *P*-values were calculated as the study was neither designed nor powered to detect statistical differences between baseline and post-treatment measurements.

In the exploratory analysis, levels of urinary biomarkers were normalized to urinary creatinine, a procedure routinely used to account for the wide between- and within-individual variation in urinary flow rates.

Results

Patient disposition

Eleven patients were enrolled in the study. During the short-term 10-week study period (8-week treatment and 2-week washout), one patient discontinued due to consent withdrawal; 10 patients completed the short-term study. Of these, five patients did not enter the extension trial as they completed the initial trial prior to the approval of the protocol amendment extending the study duration. Five patients in total completed the 108-week study duration.

Patient characteristics

Baseline characteristics ($n = 11$) are shown in Table I. Patients were a mean age of 35·2 years, were all Caucasians

Table I. Demographics and baseline characteristics for patients in the short-term 10-week study.

	Patients (n = 11)
Age, mean (range), years	35·2 (24–48)
Males:females, *n*	7:4
Caucasian, *n* (%)	11 (100)
Hispanic/Latino:other	3:8
Weight, mean ± SD, kg	61·2 ± 11·6
BMI, mean ± SD, kg/m^2	23·3 ± 4·0
Characteristic	
Serum ferritin, median (range), μg/l	2110 (840–3131)
LIC, mean ± SD, mg Fe/g dw	7·3 ± 4·0
GFR, mean ± SD, ml/min	111·5 ± 17·5
RPF, mean ± SD, ml/min	603·5 ± 94·3
FF, mean ± SD	0·19 ± 0·03
Serum creatinine, mean ± SD, μmol/l	62·0 ± 14·1
Creatinine clearance, mean ± SD, ml/min	121·7 ± 16·8

BMI, body mass index; FF, filtration fraction; GFR, glomerular filtration rate; LIC, liver iron concentration; RPF, renal plasma flow; SD, standard deviation.

and predominantly males (63·6%). All patients demonstrated iron overload at baseline, as indicated by a median (range) serum ferritin level of 2110 μg/l (840–3131 μg/l) and mean ± standard deviation (SD) LIC of 7·3 ± 4·0 mg Fe/g dw. Mean GFR, RPF and FF values were in the normal range for all patients at baseline (Table I).

Exposure to deferasirox

Overall, six (54·5%) patients were exposed to deferasirox for <3 months, two (18·2%) patients for 24 to <27 months and three (27·3%) patients received deferasirox for 27 months or longer.

Change in GFR, RPF and FF

Short-term 10-week study. Median serum ferritin level was 2110 μg/l (range 840–3131 μg/l) at baseline and 2035 μg/l (range 1100–3082 μg/l) at Week 10.

The mean GFR change at Week 8 from baseline was −15·8 ± 12·2 ml/min (−14·1%; Fig 2A). A mean decrease of −91·0 ± 53·3 ml/min (−14·9%) *versus* baseline was observed in RPF (Fig 2B). Following 2 weeks of washout (Week 10), both GFR and RPF returned to near baseline values. At Week 10, mean changes of 0·4 ± 8·7 ml/min (−0·1%) and −43·2 ± 79·6 ml/min (−6·9%) were observed for GFR and RPF, respectively, compared with baseline (Fig 2A, B). Mean ± SD FF demonstrated mild fluctuations from baseline through Week 10 (mean change at Week 8: 0·003 ± 0·03, 2·0%; Week 10: 0·01 ± 0·02, 8·2%; Fig 2C).

Mean ± SD serum creatinine concentrations increased from baseline to Week 8 by 12·6 ± 10·8 μmol/l (21·4%; Fig 3A). Following washout (Week 10), serum creatinine levels declined to close to baseline levels, as demonstrated by a mean change of 0·5 ± 7·4 μmol/l (1·9%) from baseline (Fig 3A). Similar to GFR, estimated creatinine clearance decreased at Week 8 (mean change: −21·4 ± 19·3 ml/min, −16·2%) but returned to baseline values after washout (mean change: −2·3 ± 17·3 ml/min, −1·0%; Fig 3B).

Long-term 108-week study. Median serum ferritin levels decreased from 2110 μg/l (range 840–3131 μg/l) at baseline to 1050 μg/l (range 509–3375 μg/l) at Week 108.

Among the five patients who completed the 108-week study, decreases from baseline to Week 8 were observed in GFR (mean absolute change: −9·2 ± 10·4 ml/min; −9·5%) and RPF (−105·7 ± 47·2 ml/min; −17·8%; Fig 2A, B). After the 2-week washout period at Week 10, both GFR and RPF returned to close to baseline values. Accordingly, a mean increase of 3·5 ± 11·9 ml/min (2·1%) for GFR and a mean decrease in RPF of 52·4 ± 106·9 ml/min (−9·0%) were observed at Week 10 compared with baseline.

After Week 10, treatment was re-initiated. In the following assessment at Week 52, mean GFR and RPF were decreased (mean change: −19·1 ± 8·0 ml/min, −17·7% and −155·6 ± 15·9 ml/min, −26·1%, respectively). GFR and RPF stabilized between Week 52 and Week 104. Therefore, mean changes from baseline to Week 104 were −18·4 ± 3·2 ml/min for GFR and −115·9 ± 74·3 ml/min for RPF, which were equivalent to a decrease of 17·2% and 19·6%, respectively. Following the 4-week washout period (Week 108), both measures recovered to near baseline values. Thus, at Week 108, mean change from baseline for GFR was−5·0 ± 3·5 ml/min (−4·5%) and −41·9 ± 66·5 ml/min (−7·3%) for RPF.

Mean FF showed only minor fluctuations (0·18–0·21) during the study (mean change at Week 104: 0·01 ± 0·02, 4·3%; Week 108: 0·01 ± 0·03, 5·2%; Fig 2C).

Among the five patients who completed the 108-week study, serum creatinine was elevated at Week 8 (mean change: 9·2 ± 10·0 μmol/l, 18·1%), while mean creatinine clearance decreased by −17·7 ± 22·7 ml/min (−13·7%). At Week 10 post-washout, absolute changes in both of these measures reflected a return to baseline levels (mean serum creatinine: −1·1 ± 11·0 μmol/l, 0·7%; mean creatinine clearance: −0·1 ± 26·4 ml/min, 1·6%; Fig 3A, B). Mean creatinine levels stabilized from Week 52 onwards (Fig 3A, B). At Week 104, changes in serum creatinine and creatinine clearance were 7·2% and −5·7%, respectively, compared with baseline. As observed for other measures of renal function, washout resulted in reversion of both serum creatinine and creatinine clearance to almost baseline levels at Week 108 (mean change: 1·4 ± 10·4 μmol/l, 5·3% and −5·1 ±22·4 ml/min, −2·0%, respectively).

Urinary biomarkers

Results from exploratory analyses in five patients revealed modest variations (less than one order of magnitude) in microalbumin, NGAL, KIM-1 and GST-pi, with deferasirox treatment. No apparent trend for increasing biomarker levels with time was observed in the four patients who were treated

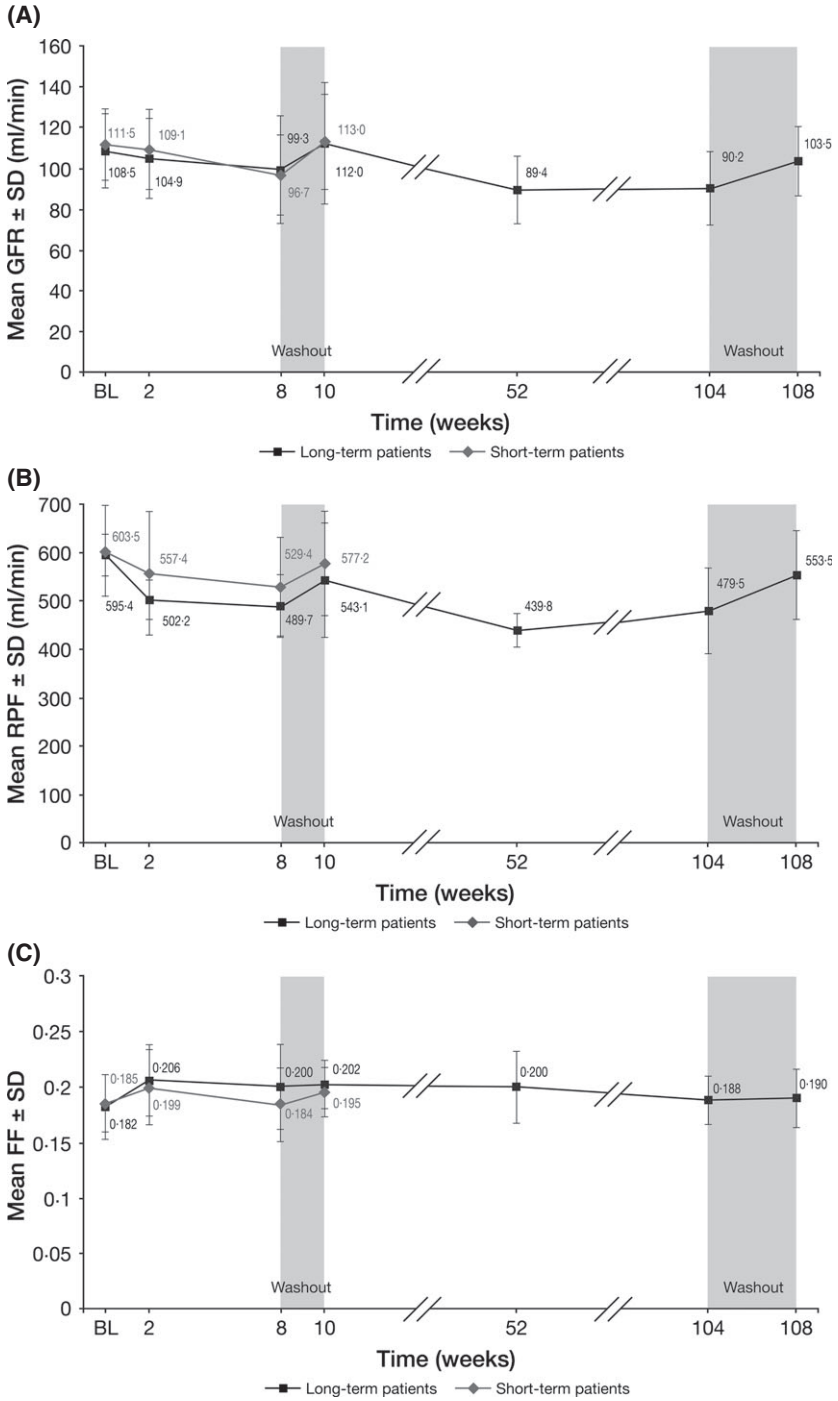

Fig 2. Mean ± SD renal haemodynamic measures over time in patients receiving short- (n = 11) and long-term (n = 5) deferasirox treatment: (A) GFR; (B) RPF; (C) FF. BL, baseline; FF, filtration fraction; GFR, glomerular filtration rate; RPF, renal plasma flow; SD, standard deviation.

for 266–342 d and in the remaining patient for whom data were available up to Week 108.

Serum creatinine, creatinine clearance and serum ferritin versus *renal and urinary markers*

As a result of the limited number of patients available for analysis, no clear trend in the relationship between changes in serum creatinine, creatinine clearance or serum ferritin and renal markers could be established. Overall, results suggest that the decrease in GFR and RPF was accompanied by a small increase in serum creatinine and a decrease in creatinine clearance. A consistent association between changes in serum creatinine and changes in urinary biomarkers was also not apparent because of the small patient sample.

Safety

All patients (n = 11) experienced at least one AE. There were no deaths or serious AEs reported during the 108-week

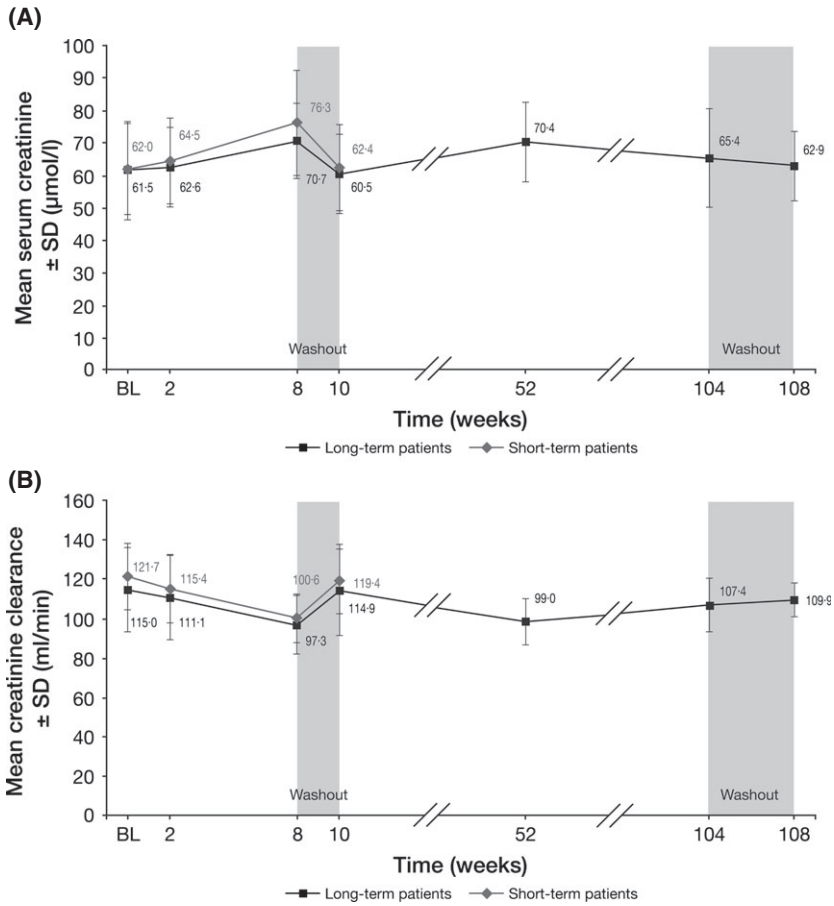

Fig 3. Mean ± SD (A) serum creatinine and (B) creatinine clearance over time in patients receiving short- (n = 11) and long-term (n = 5) deferasirox treatment. BL, baseline; SD, standard deviation.

study. Common AEs (≥10% of patients) regardless of study drug relationship included upper abdominal pain, cough, diarrhoea, oropharyngeal pain, pyrexia and rhinitis (all n = 3, 27·3%). Overall, two patients had AEs (upper abdominal pain, rash and pruritus), which were suspected by the investigator to be treatment related. In the patient with rash and pruritus, treatment with deferasirox was temporarily interrupted and then resumed once the event was resolved. The second patient had upper abdominal pain and rash, which resolved in 4 and 8 days, respectively.

There were no significant changes in haematological parameters, vital signs or aspartate aminotransferase throughout the study duration. Alanine aminotransferase in patients who completed the long-term study (n = 5) remained normal throughout, with a mean ± SD at baseline of 29·6 ± 15·5 u/l and at Week 108 of 34·4 ± 24·6 u/l.

Discussion

Patients with β thalassaemia major are at potential risk of renal dysfunction as a result of their disease, transfusional iron overload and/or chelation therapy (Ponticelli *et al*, 2010; Bhandari & Galanello, 2012). In some patients treated with deferasirox, small increases in serum creatinine – mostly mild and typically dose-dependent – have been observed (Cappellini *et al*, 2006, 2010, 2011; Galanello *et al*, 2006; Vichinsky *et al*, 2007; Porter *et al*, 2008; Pennell *et al*, 2010, 2012; Vichinsky *et al*, 2011). Although these changes are largely reversible with dose reduction and/or interruption, it is important to understand the mechanism of the effects of deferasirox, which may help us to understand whether there is a risk of any progressive worsening of renal function. In addition, preclinical studies have suggested that the renal effects of deferasirox may be due to a direct action on renal tubular cells, although these findings could not be repeated in a human cell line (Sánchez-González *et al*, 2011). This study, therefore, aimed to evaluate the short- and long-term effects of deferasirox on renal haemodynamics in patients with β thalassaemia major. Over a total study duration of 108 weeks, deferasirox was associated with a mild reversible haemodynamic effect on renal function, as measured by GFR, RPF, FF, serum creatinine and creatinine clearance. Decreases in GFR and RPF were observed at Week 8 in the short-term study and up to Week 52 in the long-term study. A similar pattern of change was noted for serum creatinine and creatinine clearance. Although there were no assessments between Week 10 and Week 52, all renal parameters were seen to stabilize between Week 52 and Week 104. Importantly, renal measures recovered to near baseline values after washout at both short- and long-term endpoints. This suggests, firstly, a reversibility of treatment effect, and, secondly, no progressive

worsening of renal function with up to 2 years of treatment with deferasirox.

In this study, there was no clear trend in the relationship between the measured renal parameters and serum creatinine or creatinine clearance, despite observations suggesting that decreases in GFR and RPF were accompanied by a small increase in serum creatinine and decrease in creatinine clearance. In addition, no consistent pattern of changes was detected when serum ferritin was plotted against GFR, RPF and FF. Other studies have also noted a lack of correlation between serum ferritin changes and changes in GFR, but have shown significant correlation between serum ferritin and *N*-acetyl beta-D-glucosaminidase (NAG) activity (Jalali *et al*, 2011). While the small sample population is a likely explanation for the observed lack of correlation, the possibility exists that an inconsistent relationship between measured parameters reflects the mild and transient effect of deferasirox on renal haemodynamics. It should also be noted that the results from this exploratory analysis are presented descriptively, as the study was neither designed nor powered to detect statistical differences between different populations.

It is interesting to note that the patient population in this study was both older (being restricted to adult patients as a result of the invasive nature of the study) and had a lower than average iron burden than the general β thalassemia population. We may speculate that these two factors increase susceptibility to renal complications in these patients; this may add value to our finding that deferasirox is associated with only a mild reversible haemodynamic effect on renal function, which is of interest to clinical practice. Furthermore, although the small sample size signals caution in the interpretation of our study findings, the observations in this study are substantiated by results from larger clinical trials (Cappellini *et al*, 2006, 2010, 2011; Galanello *et al*, 2006; Vichinsky *et al*, 2007; Porter *et al*, 2008; Pennell *et al*, 2010, 2012; Vichinsky *et al*, 2011). In the first prospective trial to monitor the long-term effects of deferasirox in children and adults with β thalassaemia, mild and non-progressive increases in serum creatinine were noted among patients who received deferasirox treatment for up to 5 years (Cappellini *et al*, 2011). The study also reported slight decreases in creatinine clearance that did not progress beyond the first 6 months of treatment (Cappellini *et al*, 2011). During the first year of this study, it was shown that the incidence of creatinine elevations was highest in patients with low transfusional iron intake who had the most dramatic decreases in LIC and serum ferritin (Cappellini *et al*, 2006), although a recent study has indicated that there is no overall increased risk of renal toxicity in deferasirox-treated patients with LIC <7 mg Fe/g dw, compared with those with LIC >7 mg Fe/g dw (Porter *et al*, 2013). Nevertheless, the occurrence of renal complications and the implications from preclinical trials advocate that continual monitoring of both renal and liver function during deferasirox treatment is carried out (Novartis Pharmaceuticals 2013; Novartis Pharmaceuticals UK Ltd, 2014) (http://www.medicines.org.uk/emc/medicine/18805/; http://www.pharma.us.novartis.com/product/pi/pdf/exjade.pdf), to ensure that risks of chelation are minimized.

Early identification of kidney damage is imperative to minimize the potential for progressive renal injury (Guo & Nzerue, 2002). Urinary biomarkers, such as GST-pi, KIM-1 and NGAL, have been shown to serve as reliable early indicators of acute kidney injury (Koyner *et al*, 2010). In this study, results from exploratory analyses of change in these urinary biomarkers with deferasirox treatment did not show significant elevations or a trend to increase over time, suggesting the absence of acute or progressive kidney damage in the small population investigated.

The safety profile of deferasirox among patients with β thalassaemia in this study was consistent with that observed in other large studies, with AEs being mainly mild-to-moderate and gastrointestinal (Cappellini *et al*, 2010, 2011). With relevance to renal function and in agreement with prior long-term reports in thalassaemia (Cappellini *et al*, 2011), none of the patients discontinued the study because of serum creatinine increases.

In conclusion, our results showed that in patients with no pre-existing renal dysfunction or disease, deferasirox appears to produce a mild effect on renal haemodynamics, which was reversible after drug interruption over the short and long term, with no progressive worsening of renal function. Despite the limited sample size, these findings contribute to accumulating evidence supporting a favourable long-term risk:benefit profile for deferasirox in the treatment of transfusional iron overload.

Acknowledgements

This study was sponsored by Novartis Pharma AG. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals. We thank Debbi Gorman and Catherine Risebro of Mudskipper Business Ltd (London, UK) for editorial assistance with this manuscript.

Authorship contributions

A Piga, S Fracchia, ME Lai, GL Forni and MD Cappellini served as investigators on this trial, enrolling patients. They were involved in the conduct of the trial, from study design to analysis plan and data interpretation. R Hirschberg advised during development of the trial protocol. A Wegener and D Habr were the sponsor study physicians and provided critical clinical expertise, and contributed to the analysis and reporting of the trial data. E Bouillaud 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.

Disclosure of conflicts of interest

A Piga: Research funding and consultancy, Novartis Pharmaceuticals; MD Cappellini: Novartis Pharmaceuticals speakers' bureau, and receiving honoraria from Novartis Pharmaceuticals and from Genzyme; S Fracchia and ME Lai: None; GL Forni: Research funding, Novartis Pharmaceuticals; R Hirschberg: Novartis advisory board and consultancy; D Habr, A Wegener and E Bouillaud: Employment, Novartis.

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