Kidney Tubular Damage Secondary to Deferasirox

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Contributor: Sebastiano Lava

Deferasirox is a first-line therapy for iron overload that can sometimes cause kidney damage. A proximal tubulopathy pattern may be observed on treatment with deferasirox. Since deferasirox-associated kidney damage is dose-dependent, physicians should prescribe the lowest efficacious dose.

deferasirox kidney tubular damage

1. Introduction

Iron overload secondary to regular blood transfusions may result in injury and dysfunction of the heart, liver, anterior pituitary, pancreas, and joints. Both parenteral iron chelation with deferoxamine and oral chelation with deferiprone or deferasirox have been shown to reduce iron overload and organ damage [1][2]. Due to its efficacy and ease of use, deferasirox 20–30 mg/kg once-daily is currently the first-line therapy for iron overload secondary to blood transfusions [1][2]. It has been known for about 10 years that an increase in circulating creatinine occurs in about one out of ten cases [3]. This tendency is most likely to occur in well-chelated patients with circulating ferritin 1000 µg/L or less [4].

2. Kidney Tubular Damage Secondary to Deferasirox

The majority (61%) of the 57 patients were ≤18 years of age (**Table 1**). Three-quarters of the cases were affected by a thalassemia syndrome. Laboratory features consistent with kidney damage were mostly observed >6 months after starting a standard dose deferasirox therapy, although this information was not available in more than half of the cases. A recurrence of the kidney damage was noted in nine of the 18 patients, who were again exposed to deferasirox (usually in a reduced dose).

Table 1. Characteristics of 57 patients 3 to 78, median 15 years of age with kidney damage on deferasirox therapy. Data are presented as median [with interquartile range] or as frequency (with percentage).

Gender		
Female, *N* (%)	27	47
Male, *N* (%)	30	53

Gender		
Age		
Years, median [interquartile range]	15 [6.7–21]	
≤18 years, *N* (%)	35	61
Underlying transfusion-dependent disease		
Thalassemia syndrome, *N* (%)	46	81
Diamond Blackfan anemia, *N* (%)	5	8.8
Allogenic stem cell transplantation, *N* (%)	3	5.3
Other conditions ◆, *N* (%)	3	5.3
Deferasirox dose ✢		
20–30 mg/kg/day, *N* (%)	46	87
31–42 mg/kg/day, *N* (%)	7	13
Duration of deferasirox therapy ✙		
≤1 month, *N* (%)	5	20
2–6 months, *N* (%)	4	16
>6 months, *N* (%)	16	64
Time to recovery after therapy withdrawal *		
Information not given, *N* (%)	37	65
≤1 week, *N* (%)	2	3.5
2–4 weeks, *N* (%)	3	5.3
>6 months, *N* (%)	5	8.8
Persistent abnormalities reported	2	3.5
Deferasirox therapy rechallenge, *N* (%)	18	32
Relapse of kidney damage, *N* (%)	9	16

◆ non-hereditary hemochromatosis, Ewing's sarcoma, sideroblastic anemia; ✢ information not available in 4 cases; ✙ information not available in 32 cases; * deferasirox therapy was not stopped in 17 cases.

Abnormal urinary findings were noted in 54 (95%), electrolyte or acid–base abnormalities in 46 (81%), and an acute kidney injury in 9 (16%) cases (**Table 2**). Abnormal urinary findings without any electrolyte or acid–base abnormality and without acute kidney injury were noted in 11 (19%) cases. The diagnosis of latent tubular damage was made in these cases. Nine (16%) cases presented with abnormal urinary findings, electrolyte or acid–base abnormalities, and acute kidney injury. The diagnosis of acute kidney injury accompanied by tubular damage was made in these cases. The remaining 37 (65%) cases presented with abnormalities in the electrolyte or acid–base balance but without any kidney injury (abnormal urinary findings were also observed in 34 out of the 37 cases). Hence, the diagnosis of overt kidney tubular damage was made in these cases. All patients with acute kidney injury (20 [19–33] years) were male. Furthermore, they were slightly but not significantly older than patients with latent (14 [11–19] years) or overt (11 [5.6–20] years) tubulopathy.

Table 2. Abnormal urinary findings and electrolyte-acid–base disorders were detected in 57 patients (27 females and 30 males 3 to 78, median 15 years of age) on therapy with oral deferasirox. Data are presented as median and interquartile range or as absolute numbers, as appropriate. Patients with latent tubulopathy, overt tubulopathy without acute kidney injury, and acute kidney injury are presented separately.

	All	Tubulopathy without Kidney Injury		Tubulopathy with Kidney Injury *
		Latent	Overt	
N	57	11	37	9
Age, years (median and IQR)	15 [6.7–21]	14 [11–19]	11 [5.6–20]	20 [18–33]
Females/males, *N*	27/30	6/5	21/16	0/9 ✙
Abnormal urinary findings, *N*	54	11	34	9
Renal glucosuria, *N*	34	2	23	9
Tubular proteinuria ✝, *N*	21	8	16	2
Excessive total proteinuria, *N*	17	1	11	5
Generalized aminoaciduria, *N*	9	1	4	4
Electrolyte-acid–base disorders, *N*	46	-	37	9
Metabolic acidosis, *N*	38 ✿	-	31	7
Hypophosphatemia, *N*	35	-	27	8
Hypokalemia, *N*	24	-	18	6
Hypouricemia, *N*	11	-	7	4
Hypocalcemia, *N*	6	-	6	0

	All	Tubulopathy without Kidney Injury		Tubulopathy with Kidney Injury *
		Latent	Overt	
Hyponatremia, *N*	3	-	1	2

* Stage I in 3, stage II in 5 and stage III in 1 case; ✿ anion gap normal in all cases (N = 13) with this information; ✙ acute kidney injury significantly more common in males than in females ($p < 0.02$); ✢ ß2-microglobulin excretion in all 21 cases.

The kidney tubular damage associated with oral deferasirox therapy may present in three ways: (a) abnormal urinary findings consistent with latent tubular damage; (b) overt acid–base or electrolyte abnormalities; and (c) acute kidney injury (always associated with abnormal urinary findings and with an electrolyte or acid–base imbalance).

The kidney tubular damage caused by deferasirox characteristically presents with renal glucosuria, excessive $ß_2$-microglobulin excretion, generalized aminoaciduria, non-gap metabolic acidosis, hypophosphatemia, and hypouricemia. Hence, these data suggest the existence of a proximal tubular disturbance. Proximal tubular defects are typically observed on treatment with aminoglycosides, nucleotide reverse transcriptase inhibitors, or platinum compounds and result from mitochondrial toxicity [5][6]. No kidney damage was so far reported on treatment with other iron chelators such as deferiprone or deferoxamine [2][7]. These clinical observations are supported by in vitro studies: it was found that deferasirox, but not other chelators, induces a dramatic swelling of mitochondria and decreases the cellular ATP content [8]. Iron being essential for kidney tubular cells, it is currently assumed that deferasirox associated tubular damage results from excessive chelation of iron within these cells, which is likely superior to that observed with other chelators [9]. Furthermore, the kidney damage caused by deferasirox is likely dose-dependent [9]. Finally, pharmacogenetics might be a relevant determinant of deferasirox toxicity [9][10].

In this analysis, most cases with acid–base or electrolyte abnormalities simultaneously presented with urinary abnormalities. Furthermore, all cases with kidney injury concurrently presented with an acid–base or electrolyte imbalance and with urinary abnormalities. It is therefore tempting to assume that the latent tubulopathy represents the early stage, the overt tubulopathy the middle stage, and finally the manifest acute kidney injury the advanced stage of damage induced by deferasirox (**Figure 1**). This hypothesis deserves confirmation in longitudinal studies.

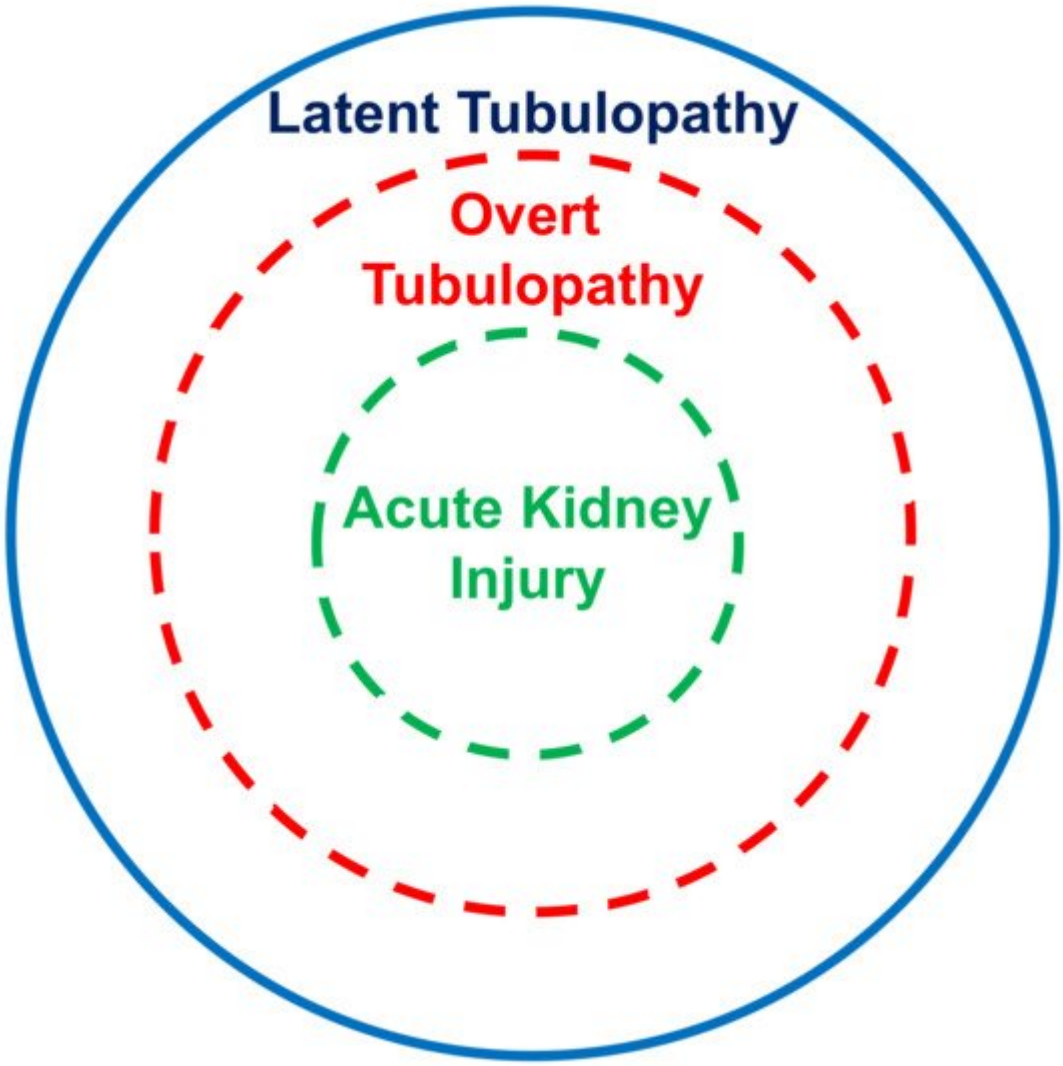

Figure 1. Suggested stratification of the kidney damage associated with deferasirox therapy.

It has been speculated but not proven that iron overload may per se induce kidney damage [1][2]. Furthermore, sickle cell disease and perhaps also some other transfusion-dependent conditions may cause kidney abnormalities [11].

3. Conclusions

Aminoglycoside-class antimicrobials, nucleotide reverse transcriptase inhibitors, and platinum compounds occasionally cause a dose- and time-related kidney disease. Similar damage may be observed on treatment with the iron-chelating agent deferasirox but not with deferoxamine or deferiprone. Deferasirox-associated kidney damage is dose-dependent and more likely to occur when iron stores are low. It has therefore been recommended [4][9] that physicians prescribe the lowest possible dose to achieve a satisfactory iron burden and consider discontinuing therapy if circulating ferritin is 1000 µg/L or less.

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