Original Article

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Effect of Deferasirox Dose and Treatment Duration on Frequency of Proteinurea and Renal Functions in Patients With Thalassemia Major

Sarbay and Akbalık Kara. Effect of Deferasirox on Proteinurea and Renal Functions in Patients With Thalassemia Major

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ABSTRACT

BACKGROUND/AIMS: Nephrotoxicity may develop in thalassemia major because of the disease and deferasirox treatment. The aim of this study is to investigate the effect of deferasirox dose and treatment duration on frequency of proteinuria and renal functions.
MATERIALS AND METHODS: Patients with thalassemia major who underwent regular transfusion and using deferasirox as an iron chelator were included in the study. According to the international follow-up protocols, screening tests (urea, creatinine, electrolytes, ferritin, complete urine analysis, spot urine protein-creatinine ratio) which are examined every 3 months, were recorded for once for each patient (March 2018-June 2018).
RESULTS: 66 patients were included in this study (35 boys and 31 girls). The mean age was 9.89 ± 4.67 years and the mean age of starting to transfusion was 7.86 ± 7.89 months. The mean duration of treatment with deferasirox was 7.12 ± 3.94 years. Significant difference was found in incidence of proteinuria when deferasirox dose was higher than 40 mg / kg / day. When deferasirox treatment duration was evaluated, creatinine values were significantly lower in patients with treatment duration longer than 5 years (P = 0.001).
CONCLUSION: Instead of increasing the dose of deferasirox, switching to combined therapy may be more effective and safer in terms of side effects.

Keywords: Deferasirox, proteinuria, thalassemia major, nephrotoxicity

INTRODUCTION

Beta-thalassemia syndromes are genetic hematologic disorders characterized by chronic hemolytic anemia. The main pathophysiological disorder is ineffective erythropoiesis due to a relatively increased alpha-globin chain imbalance versus decreased and completely stopped B-globin synthesis (1). The clinical spectrum of the disease varies from transfusion-dependent anemia to thalassemia minor. Thalassemia is common in the Mediterranean Region and is an important public health problem. After the development of thalassemia screening programs in recent years, the number of patients with thalassemia has been controlled. Screening programs in combination with prenatal genetic testing and genetic counselling has decreased the number of thalassemia major births. Regular transfusions, chelation therapy, and experience of the disease have caused to a significant increase in life expectancy in patients with thalassemia (1-3).

In thalassemia major (TM), with increased life expectancy, cardiopulmonary system, endocrine, hepatic and renal complications can be seen more commonly. Tubular and glomerular disorders are the most common pathologies in renal complications. Chronic anemia, oxidative stress and iron chelators are thought to be the most common etiologic causes of nephrotoxicity. Deferasirox (DFX) is the most commonly used agent in iron chelators (4). One of the most important side effects is nephrotoxicity. It is known that high doses of DFX causes renal tubular damage in animal experiments (5,6). The aim of this study is to investigate the effect of DFX dose and treatment duration on frequency of proteinuria and renal functions with using primer screening tests.

MATERIALS AND METHODS

Patients with TM who underwent regular transfusion (15 ml / kg, every 3 weeks) and using deferasirox as an iron chelator were included in the study. Age, gender, diagnosis time, transfusion starting time, duration of treatment, deferasirox dose, genetic mutation analysis, blood counts, liver-renal function tests (urea, creatinine, electrolytes, ferritin, complete urine analysis, spot urine protein-creatinine ratio) were evaluated retrospectively. According to the international TM follow-up protocols, the control laboratory values which are examined every 3 months, were recorded for once for each patient (March 2018-June 2018). Average and standard deviation values were calculated. Abdominal ultrasonography results of the patients were checked for anatomic and morphologic renal pathologies. Routine pediatric cardiology and pediatric endocrinology consultations were performed.

Upper limits of the creatinine are considered 0.9 mg/dL for ages 3 to 18 years, 0.7 mg/dL for under age 3. Urine protein / creatinine ratio in the morning was 0.5 mg / gram creatinine below 2 years of age and 0.2 mg / gram creatinine limit for children over 2 years of age (7). For the urine protein method, benzethonium chloride was used by turbimetric procedure. Creatinine value was studied biochemically with Architect c1600 device. Normal GFR values were considered to be 140 ± 30 for 2-12 years of age, 133 ± 27 for 13-21 years of age in boys and 126 ± 22 for 13-21 years of age in girls (8). Renal function test results and frequency of proteinuria were compared according to the dose of deferasirox and duration of treatment.

In generally the starting dose of deferasirox was 20 mg / kg / day, starting time is 2 years old age and the serum level of ferritin should be > 1000 ng / ml. (Exjade; Novartis) Dose increase

up to 40 mg / kg / day depending on ferritin levels is tolerable if there are no complications (2). The FDA and European Medicines Agency have recommended doses up to 40 mg /kg / day in patients that inadequately chelated with lower doses. Above 40 mg / kg / day are not approved (9). Therefore, we set the deferasiroks dose limit of 40 mg / kg / day in our study.

Patients who did not receive deferasirox treatment regularly and those who received combined chelator treatment were excluded from the study. We did not have the possible utility of other biomarkers to detect kidney injury and renal functions for the detailed investigation. For this reason only screening tests of TM protocols were used for the study.

This retrospective study was approved by local ethics committee in 2019 (Protocol number: 2019-235). Approval statement for participation received from the Legal Authorized Representatives of the participants

STATISTICAL ANALYSIS

The normality of distribution of continuous variables was tested by Shaphiro Wilk's test. Student t test (for normal data) and Mann-Whitney U test (for non-normal data) was used for comparison of two independent groups and Chi-square test was used to evaluate between categorical variables. SPSS for Windows version 22.0 and a p value <0.05 was accepted as significant. All analyses were conducted with the use of Statistical Product and Service Solutions (SPSS 22.0) software.

RESULTS

Total number of 66 patients were included in this study (35 boys and 31 girls). The mean age was 9.89 ± 4.67 years and the mean age at diagnosis and starting to transfusion was 7.86 ± 7.89 months. The mean duration of treatment with DFX was 7.12 ± 3.94 years. General characteristics and laboratory mean values of the patients are given in Table-1. Significant difference was found in terms of incidence of proteinuria when deferasirox dose was higher than 40 mg / kg / day. (Table-2). When treatment duration was evaluated (Table-3), creatinine values were significantly lower in patients with treatment duration longer than 5 years ($P = 0.001$). There were no findings suggestive of renal tubular nephropathy such as hypophosphatemia, low bicarbonate level and acidosis in routine blood biochemistry controls. No anatomic and morphological findings were detected on urinary system ultrasound.

Genetic mutation analysis was studied in 37 of 66 patients, and the most common mutation (67.6%) was the homozygous mutation of IVS I-110. In our study, no comparison and interpretation could be made between the genetic results and renal function tests.

DISCUSSION

In patients with TM, renal involvement can be occurred due to chronic anemia and iron overload (5). DFX is the most commonly used oral chelator in the world. A slight increase in serum creatinine levels is the most often toxic impact of DFX. Nevertheless, DFX rarely cause renal insufficiency requiring dialysis (3). Generally, nephrotoxicity is reversible and normalization of renal function is observed after cessation of treatment. The most affected area is the proximal tubules and the pathophysiology is not fully known (10). Although DFX is generally well tolerated, a moderate, dose-dependent and non-progressive increase in creatinine was reported in 36% of patients in clinical trials (11). In a retrospective study, treatment was terminated due to creatinine elevation in 7 of 72 patients (12). DFX-induced nephrotoxicity is thought to be more frequent in adults with accompanying diabetes (10,13). Diabetes mellitus (DM) was not detected in the endocrinological examinations of our patients.

We thought that the reason why creatinine values did not increase in contrast to adult studies might be related to the absence of DM in our patients.

Use of nephrotoxic drugs in combination with high doses of DFX increases renal involvement. After the deferasirox initiation, serum creatinine levels must be controlled regularly. However patients with B thalassemia major should be followed up with spot urine protein/creatinine ratio measured monthly for proteinuria. It is known that urinary protein excretion increase in beta thalassemia major compared to normal patients. Proteinuria should be considered, if urine protein/creatinine ratio is ≥0.6 (3). Aldudak et al. (14) has determined this limit as 0.7. In a study conducted in our country, proteinuria due to deferasirox was observed in 7 of 37 patients (19%). It was observed that as the DFX dose increased, the probability of proteinuria was increased (15). In our study, the frequency of proteinuria was found to be significantly higher in the group with DFX dose above 40 mg / kg / day. In one patient whose dose of DFX increased to 40 mg/kg/day, proteinuria was detected in the urine analysis and spot urine protein/creatinine ratio increased to 2.5. High creatinine levels, low C3-C4 levels and hypoalbuminemia were not detected in laboratory tests and no clinical findings were observed on physical examination. Dubourg et al. (16) showed that tubular damage could be stopped with decreasing drug dosage. In our patient, proteinuria was not detected in the urine analysis at the 2nd week after discontinuation of the drug.

Although renal failure was not reported during DFX therapy in previous studies, development of renal dysfunction was observed. Renal dysfunction is mostly in the form of tubulopathy and resolved after discontinuation of DFX treatment (17-21). In addition to this, although tubulopathy is mostly reversible, the possibility of chronic tubular damage, interstitial fibrosis and chronic renal disease should be kept in mind. Glomerular and tubular damage develops over time due to chronic toxic effects of the disease and chelators. It is thought that decrease in the glomerular filtration rate would cause increasing in serum creatinine levels (16). In contrast to previous clinical trial, in our study, creatinine values were found to be significantly lower in patients with treatment duration longer than 5 years. We think that decrease in creatinine may also be a sign of hyper filtration as a result of thalassemia and inadequate transfusions, rather than due to the DFX treatment.

In recent years, some studies suggest that combined oral chelation with deferiprone (DFP) (Ferriprox-Chiesi) and DFX has better efficacy than either drug used alone. In these studies there were no problems with adverse effects and drug tolerance in combined therapy as safe dose range is maintained (22,23). It is a fact that; DFX, with its daily single dose use and its tablet form, which has been used in recent years, is the iron chelator frequently preferred by patients and their relatives as well as physicians. However, its renal toxicity is well-enlightened today and the use of high doses is one of the biggest risk factors for this. (24). Desferrioxamine (DFO) is a non-feasible option for iron-chelation in a large majority of patients in developing countries because of the high cost, coupled with the need for continuous infusion. Monotherapy with DFP or DFX may cause inadequate control, especially in severe iron-loaded patients. Combination of DFP and DFX is a potential alternative especially to avoid high dose toxicities (25).

Limitations of the Study

The main limitation of our study was the low number of patients especially who were received a dose above 40 mg / kg / day. The fact that it is a single center study was the main reason for the limited number of patients.

CONCLUSION

DFX is an appropriate drug in terms of use and efficacy, but proteinuria and other renal complications may be seen in dose increase. In patients with high ferritin levels and iron overload, we think that instead of increasing the dose of DFX, switching to combined therapy may be more effective and safer in terms of side effects.

MAIN POINTS

1. Nephrotoxicity may develop in thalassemia major because of the disease and deferasirox treatment.
2. The frequency of proteinuria is significantly higher when deferasirox dose is increased above 40 mg / kg / day.
3. In patients with high ferritin levels and iron overload, instead of increasing the dose of DFX, switching to combined therapy may be more effective and safer in terms of side effects.

ETHICS

Ethics Committee Approval: This retrospective study was approved by local ethics committee in 2019 (protocol number: 2019-235).
Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.S., M.A.K., Design: H.S., M.A.K., Supervision: H.S., M.A.K., Data Collection and/or Processing: H.S., M.A.K., Analysis and/or Interpretation: H.S., M.A.K., Literature Search: H.S., M.A.K., Writing: H.S., M.A.K., Critical Reviews: H.S., M.A.K.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.
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Table 1: Descriptive statistics

	(n=66)
Gender (n(%))	
Boys	35 (53.0)
Girls	31 (47.0)
	Mean±SD
Age	9.89 ± 4.67
Diagnosis and starting to transfusions (month)	7.86 ± 7.89
Treatment time (year)	7.12 ± 3.94
Body mass (kg)	30.12 ± 13.33

Deferasirox (mg/kg)	30.3 ± 4.57
Ferritin (ng/ml)	2839.82 ± 1907.74
Leucocyte (/mm^3)	11238.68 ± 7112.87
Hemoglobin (gr/dl)	9.27 ± 1.31
Thrombocyte count (/mm^3)	405984.85 ± 212351.99
AST (U/L)	37.33 ± 28.02
ALT (U/L)	31.71 ± 34.44
Urea (mg/dl)	28.09 ± 9.08
Creatinine (mg/dl)	0.48 ± 0.07
Urine density	1012.2 ± 5.85
Spot urine protein/creatinine	0.33 ± 0.3
GFR (ml/min/1.73 m^2)	156.36 ± 29.15

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GFR: Glomerular filtration rate; SD: Standart deviation

Table 2: Comparison of renal function tests of the patients according to deferasirox dose

	Deferasirox dose mg/kg/day		
	<40 (n=61)	≥40 (n=5)	
Variables	**Mean±SD**	**Mean±SD**	P
Urea (mg/dl)	27.8 ± 7.82	31.6 ± 20.11	0.689§
Creatinine	0.49 ± 0.07	0.46 ± 0.08	0.448‡
Urine density	1012.2 ± 5.92	1012.2 ± 5.63	0.999‡
Spot urine protein/creatinine	0.3 ± 0.12	0.69 ± 1.01	0.907§
GFR (ml/min/1.73m2)	157.33 ± 29.91	144.6 ± 14.08	0.479§
	n(%)	**n(%)**	
Proteinuria			
Negative	60(98.4)	4(80.0)	
Positive	1(1.6)	1(20.0)	**0.021¶**

SD: Standart deviation
§: Mann whitney u test, ‡: Student t test, ¶: Chi-square test.
*Significant at 0.05 level.

Table 3: Comparison of renal function tests according to deferasirox treatment duration

	Treatment time		
	≤5 years (n=25)	>5 years (n=41)	
Variables	**Mean±SD**	**Mean±SD**	P
Urea (mg/dl)	27.8 ± 7.82	31.6 ± 20.11	0.169§
Creatinine (mg/dl)	0.49 ± 0.07	0.46 ± 0.08	**0.001*‡**
Urine density	1012.2 ± 5.92	1012.2 ± 5.63	0.828‡
Spot urine protein/creatinine	0.3 ± 0.12	0.69 ± 1.01	0.173§
GFR (ml/min/1.73m^2)	157.33 ± 29.91	144.6 ± 14.08	**0.001*§**
	n(%)	**n(%)**	
Proteinuria			
Positive	24(96.0)	40(97.6)	0.720¶
Negative	1(4)	1(2.4)	

GFR: Glomerular filtration rate; SD: Standart deviation
§: Mann whitney u test, ‡: Student t test, ¶: Chi-square test.
*Significant at 0.05 level.