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The Effect of Deferasirox Dose and Treatment Duration on Frequency of Proteinuria and Renal Functions in Patients with Thalassemia Major

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Abstract

BACKGROUND/AIMS: Nephrotoxicity may develop in thalassemia major (TM) because of the disease and deferasirox (DFX) treatment. The aim of this study was to investigate the effect of deferasirox dose and treatment duration on the frequency of proteinuria and renal functions.

MATERIALS AND METHODS: Patients with TM who were undergoing regular transfusion and were using DFX as an iron chelator were included in this study. According to the international follow-up protocols, screening tests (urea, creatinine, electrolytes, ferritin, complete urine analysis, and spot urine protein-creatinine ratio) which are examined every 3 months, were recorded once for each patient (March 2018-June 2018).

RESULTS: Sixty-six patients were included in this study (35 boys and 31 girls). Their mean age was 9.89±4.67 years and the mean age of starting transfusion was 7.86±7.89 months. The mean duration of treatment with DFX was 7.12±3.94 years. A significant difference was found in the incidence of proteinuria when the DFX dose was higher than 40 mg/kg/day. When DFX treatment duration was evaluated, creatinine values were significantly lower in those patients with a treatment durations longer than 5 years (p=0.001).

CONCLUSION: Instead of increasing the dose of DFX, 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 determined. Screening programs in combination with prenatal genetic testing and genetic counselling has decreased the number of thalassemia major (TM) births. Regular transfusions, chelation therapy, and experience with this disease have led to a significant increase in the life expectancy of those patients with thalassemia.[1-3]

In 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.

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Deferasirox (DFX) is the most commonly used agent in iron chelators.[4] One of its most important side effects is nephrotoxicity. It is known that high doses of DFX cause renal tubular damage in animal experiments.[5,6] The aim of this study was to investigate the effect of DFX dosage and treatment duration on the frequency of proteinuria and renal functions by using primer screening tests.

MATERIALS AND METHODS

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

The upper limits of the creatinine are considered to be 0.9 mg/dL for the ages 3 to 18 years, and 0.7 mg/dL for under the age of 3 years. The urine protein/creatinine ratio limit in the morning is 0.5 mg/gram creatinine below 2 years of age and 0.2 mg/gram creatinine for children over 2 years of age.[7] For the urine protein method, benzethonium chloride was used via the turbimetric procedure. The creatinine value was studied biochemically with the Architect c1600 device. Normal glomerular filtration rate (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 the frequency of proteinuria were compared according to the dose of DFX and its duration of treatment.

In general, the starting dose of DFX is 20 mg/kg/day, the starting time is 2 years of age and the serum level of ferritin should be >1,000 ng/mL (Exjade; Novartis). The dosage can increase up to 40 mg/kg/day depending on ferritin levels if there are no complications.[2] The FDA and European Medicines Agency have recommended doses up to 40 mg/kg/day in patients who inadequately chelate with lower doses. Doses above 40 mg/kg/day are not approved.[9] Therefore, we set the DFX dose limit at 40 mg/kg/day in our study.

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

This retrospective study was approved by the Diyarbakır University of Health Sciences Gazi Yaşargil Training and Research Hospital Local Ethics Committee in 2019 (approval number: 2019-235). An approval statement for participation was received from the parents or legal guardians of the participants.

Statistical Analysis

The normality of distribution of continuous variables was tested by the Shaphiro-Wilk's test. Student's t-test (for normal data) and Mann-Whitney U test (for non-normal data) was used for comparisons of two independent groups and the chi-square test was used to evaluate between categorical variables. The SPSS for Windows version 22.0 was used 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

A total number of 66 patients were included in this study (35 boys and 31 girls). Their mean age was 9.89±4.67 years and their mean age at diagnosis and starting transfusion was 7.86±7.89 months. The mean duration of treatment with DFX was 7.12±3.94 years. The general characteristics and laboratory mean values of the patients are given in Table 1. A significant difference was found in terms of the incidence of proteinuria when the DFX dose was higher than 40 mg/kg/day (Table 2). When treatment duration was evaluated (Table 3), creatinine values were significantly lower in those patients with a 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 or morphological findings were detected on urinary system ultrasound.

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

DISCUSSION

In patients with TM, renal involvement can occur due to chronic anemia and iron overload.[5] DFX is the most commonly used oral chelator in

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 transfusions (months)	7.86±7.89
Treatment time (years)	7.12±3.94
Body mass (kg)	30.12±13.33
Deferasirox (mg/kg)	30.3±4.57
Ferritin (ng/mL)	2,839.82±1,907.74
Leucocyte (/mm^3)	11,238.68±7,112.87
Hemoglobin (gr/dL)	9.27±1.31
Thrombocyte count (/mm^3)	405,984.85±212,351.99
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	1,012.2±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: standard deviation.

the world. A slight increase in serum creatinine levels is the most often seen 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 the cessation of treatment. The most affected area is the proximal tubules but the pathophysiology is not fully known.[10] Although DFX is generally well tolerated, a moderate, dose-dependent and non-progressive increase in creatinine has been reported in 36% of patients in clinical trials.[11] In a retrospective study, treatment was terminated due to creatinine elevation in 7 out 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 DFX initiation, serum creatinine levels must be checked regularly. However, patients with B TM should be followed up with spot urine protein/creatinine ratio measurements monthly for proteinuria. It is known that urinary protein excretion increases in beta TM compared to normal patients. Proteinuria should be considered if the urine protein/creatinine ratio is ≥0.6.[3] Aldudak et al.[14] determined this limit to be 0.7. In a study conducted in our country, proteinuria due to DFX was observed in 7 out of 37 patients (19%). It was noted that as the DFX dose increased, the probability of proteinuria increased.[15] In our study, the frequency of proteinuria was found to be significantly higher in the group with a DFX dose above 40 mg/kg/day. In one patient whose dose of DFX was increased to 40 mg/kg/day, proteinuria was detected in the urine analysis and their 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 by decreasing the drug dosage. In our patient, proteinuria was not detected in the urine analysis at the 2nd week after the discontinuation of the drug.

Although renal failure was not reported during DFX therapy in previous studies, the development of renal dysfunction was observed. Renal dysfunction is mostly in the form of tubulopathy and resolved after the 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 the chronic toxic effects of the disease and chelators. It is thought that a

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	1,012.2±5.92	1,012.2±5.63	0.999‡
Spot urine protein/creatinine	0.3±0.12	0.69±1.01	0.907§
GFR mL/min/1.73 m^2	157.33±29.91	144.6±14.08	0.479§
	n (%)	**n (%)**	
Proteinuria			
Negative	60 (98.4)	4 (80.0)	**0.021¶**
Positive	1 (1.6)	1 (20.0)	

SD: standard deviation, §: Mann-Whitney U test, ‡: Student's t-test, ¶: chi-square test.
*Significant at 0.05 level, GFR: glomerular filtration rate.

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	1,012.2±5.92	1,012.2±5.63	0.828‡
Spot urine protein/creatinine	0.3±0.12	0.69±1.01	0.173§
GFR (mL/min/1.73 m^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: standard deviation, §: Mann-Whitney U test, ‡: Student's t-test, ¶: chi-square test, *significant at 0.05 level.

decrease in the GFR would cause an increase in serum creatinine levels.[16] In contrast to previous clinical trials, in our study, creatinine values were found to be significantly lower in those patients with a treatment duration longer than 5 years. We think that a 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 have suggested 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 a 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 most frequently preferred by patients and their relatives as well as physicians. However, its renal toxicity is well-known today and its use in high doses is one of the biggest risk factors for this.[24] Desferrioxamine is a non-feasible option for iron-chelation in a large majority of patients in developing countries because of its high cost, coupled with the need for continuous infusion. Monotherapy with DFP or DFX may cause inadequate control, especially in severe iron-loaded patients. The combination of DFP with DFX is a potential alternative especially so as to avoid high dose toxicities.[25]

Study Limitations

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

CONCLUSION

DFX is an appropriate drug in terms of its use and efficacy, but proteinuria and other renal complications may be seen in higher doses. 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

• Nephrotoxicity may develop in thalassemia major because of the disease and deferasirox treatment.

• The frequency of proteinuria is significantly higher when the deferasirox dose is increased above 40 mg/kg/day.

• 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 the Diyarbakır University of Health Sciences Gazi Yaşargil Training and Research Hospital Local Ethics Committee in 2019 (approval number: 2019-235).

Informed Consent: An approval statement for participation was received from the parents or legal guardians of the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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