The questioning for routine monthly monitoring of proteinuria in patients with β-thalassemia on deferasirox chelation

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ABSTRACT

Background: Iron chelation therapy is one of the mainstays of the management of the patients with β-thalassemia (BT) major. Deferasirox is an oral active iron chelating agent. Proteinuria is one of the potential renal adverse effects of deferasirox, and monthly follow-up for proteinuria is suggested by Food and Drug Administration and European Medicine Agency.

Methods: We aimed to investigate the necessity for monthly monitoring for proteinuria among patients with BT on deferasirox. A retrospective laboratory and clinic data review was performed for patients with BT major or intermedia who were treated with deferasirox chelation therapy. All patients were monitored for proteinuria for every 3 or 4 weeks after the initiation of deferasirox with serum creatinine and spot urine protein/creatinine ratios.

Results: The median follow-up time of the 37 (36 BT major and one BT intermedia) patients was 44 months. Seven patients (18.9%) developed significant proteinuria (ratio ≥ 0.8). Of the 1490 measurements, 12 tests (0.8%) were proteinuric. Urine proteinuria resolved in all of the patients during the follow-up. The risk of proteinuria was higher at ages below a cut-off point of 23 years (p = 0.019). Patients, who were on deferasirox at doses above a cut-off dose of 29 mg/kg/day, were found to have higher risk of proteinuria development (p = 0.004).

Conclusion: Proteinuria resolves without any complication or major intervention according to our results. Potentially more risky groups (age below 23 years old and receivers above a dose of 29 mg/kg/day) might be suggested to be followed monthly, besides monitoring all of the patients.

KEYWORDS

Deferasirox; proteinuria; thalassemia

Introduction

Iron accumulation is the major concern in patients with β-thalassemia (BT) major or intermedia [1]. Ineffective erythropoiesis-induced iron absorption and chronic erythrocyte transfusions result in iron overloading, and the liver, heart, and endocrine organs are the major sites of iron accumulation [2–4]. Therefore, iron chelation therapy is one of the mainstays of BT management [4]. Deferasirox (marketed as Exjade⁴, Novartis Pharma AG, Switzerland) is a potent iron chelator and accepted as a first-line therapy for blood transfusion-related iron overloading [5,6]. Since its approval by Food and Drug Administration (FDA) in 2005, it has been prescribed to more than 150 000 patients a year [5]. Nephrotoxicity is one of the most common adverse effects of deferasirox that develops in more than one in 10 patients [5]. Renal adverse events due to the use of deferasirox are renal failure, acute kidney injury, glomerulonephritis, interstitial nephritis, and renal tubulopathy [5]. Increase of serum creatinine level is the most frequent nephrotoxic event associated with deferasirox [7–9]. Thus, measurement of serum creatinine levels weekly during the first month of treatment and monthly thereafter is a routine of deferasirox follow-up. Monthly monitoring of proteinuria in BT patients treated with deferasirox has been recommended by both FDA and European Medicine Agency (EMA), but there has not been any action suggested for proteinurea changes [5]. In our study, we aimed to question the effectiveness and necessity of monthly monitoring of proteinuria in BT patients treated with deferasirox and determine medical interventions and their consequences in case of proteinuria.

Patients and methods

A retrospective clinic and laboratory data review was performed for patients with BT major or intermedia who were treated with deferasirox in a single centre between October 2007 and July 2014. All patients’ serum creatinine and urinary protein/creatinine values were recorded before the initiation of deferasirox. All of the patients were evaluated for glomerular filtration rates prior to deferasirox initiation, and all of the patients included in the current study had normal glomerular filtration rate values prior to deferasirox initiation. As a routine modality during the deferasirox treatment, patients were checked every 3 to 4 weeks for renal...
and liver functions by serum biochemistry and urinary protein/creatinine level from spot urine analysis. All monthly urinary protein/creatinine ratio results were noted. Proteinuria is accepted if in spot urine protein/creatinine ratio is $\geq 0.8$, because urinary protein excretion is higher than normal in patients with BT [5] and Aldudak et al. revealed mean protein/creatinine ratio 0.7 in patients with BT [10]. If pathologic proteinuria was detected, clinical manipulations for proteinuria were noted. Statistical analyses were carried out with IBM SPSS Statistics for Windows, Version 21.0 software (Armonk, NY: IBM Corp). Mann–Whitney U-test was used to compare two groups. Receiver operating characteristic (ROC) curve was drawn to determine cut-off points for age and deferasirox dose. The point, in which sensitivity and specificity values were maximum, was chosen as the best cut-off point.

**Results**

In this study, data of 37 BT patients (15 males and 22 females, using deferasirox between October 2007 and July 2014) were included. Thirty-six of patients were diagnosed to have BT major and one had BT intermedia. The median age of patients was 21.9 years (range: 4.8–39.2) (Table 1). Data for proteinuria were obtained retrospectively for 44 months (range 9–78 months). In each follow-up visit, the patients were requested to give urine samples; however, despite 1987 orders, 1490 of the urine samples were delivered to the laboratory, and test compliance was 75%. Urine protein/creatinine values were calculated from 1490 urine samples, and 12 incidents of proteinurea (0.8% of the samples) were detected in seven patients (19% of the patients) (four males, three females). Distribution of protein/creatinine values is given in Table 1. The patients below the age of 23 years were found to have higher risk of developing at least one incidence of proteinurea (cut-off: 23 years, sensitivity: 100.0%, specificity: 56.7%, $p = 0.019$). In addition, the patients using higher doses of deferasirox were prone to develop proteinurea compared to those using lower doses (cut-off: 29 mg/kg/day, sensitivity: 71.4%, specificity: 84.3%, $p = 0.004$) (Figure 1). Moreover, at the time of proteinurea development, the serum creatinine levels of the patients were found to be increased (median increase: 50%); however, serum creatinine levels were in the normal range for each patient. Three proteinurea attacks subsided after one week of drug-free interval. The rest of the attacks were self-limiting, and urine protein/creatinine levels decreased after 1–3 follow-up visits without any interventions. None of the 12 incidents required hospitalization. Serum creatinine levels measured before the initial deferasirox dose did not show any statistically significant difference between the patients who developed proteinurea and those who did not ($p = 0.078$).

| Table 1. General characteristics of patients and distribution of protein/creatinine values. |
|---------------------------------------------------------------|
| **Diagnosis** | **$n$ (%) or median (range)** |
| Thalassemia major | 36 |
| Thalassemia intermedia | 1 |
| Age (years) | 21.9 (4.8–39.2) |
| Female/male | 22/15 |
| Total number of urine samples | 1490 |
| Urine samples with proteinuria | 12 (0.8) |
| Distribution of protein/creatinine ratios | |
| $<0.2$ | 771 (51.7%) |
| $0.2 \leq c <0.6$ | 672 (45.1%) |
| $0.6 \leq c <1$ | 40 (2.7%) |
| $c \geq 1$ | 7 (0.5%) |

![Figure 1. ROC curve of age (a) and deferasirox dose (b).](image-url)
Discussion

Patients with BT major and intermedia may have renal dysfunction secondary to chronic anemia and iron overload. Renal hyperfiltration, hypercalciuria, and proteinuria are common renal problems that might be seen in patients with BT [11]. Iron chelators add additional risks for nephrotoxicity in patients with BT. Deferasirox is a potent and widely used iron chelator that has been used for a decade [6]. Mild increase in serum creatinine levels is the main nephrotoxic effect of deferisirox. However, deferasirox nephrotoxicity may result in renal failure with dialysis requirement as well [5]. Generally, nephrotoxicity of deferasirox is reversible, and improvement in renal functions can be provided after the cessation of therapy [5,12]. The main site for deferasirox nephrotoxicity is renal proximal tubules, and the underlying mechanism of toxicity could not be understood exactly yet [5]. In a previous study by Unal et al., decompartmentalization of iron to kidneys from other organs with deferasirox use could not be demonstrated [13]. Deferasirox-related Fanconi syndrome generally occurs in younger patients (≤16 years) and elderly patients (≥65 years). Other risk factors for nephrotoxicity development are higher doses of deferasirox, pre-existing conditions that increase renal impairment probability, use of concomitant nephrotoxic drugs, and UDP glucuronosyltransferase 1 polymorphisms [5,14,15].

Serum creatinine levels were suggested to be checked weekly during the first month of deferasirox initiation and monthly thereafter. Renal tubular impairment in patients treated with deferasirox has been monitored via suggested monthly urinary protein measurements [5]. However, there are not enough data about recommendations for the patients who developed proteinuria.

In our study, we retrospectively analyzed long-term (mean 44 months) follow-up of patients with BT for proteinuria. FDA has been recommended accepting proteinuria in patients with thalassemia if protein/creatinine ratio is >0.6 [5]. In a study from Turkey, Aldudak et al. [10] revealed mean protein/creatinine ratio 0.7 in patients with β-thalassemia. In our study, we assumed the threshold of proteinuria in thalassemic patients if protein/creatinine ratio was ≥0.8. Proteinuria was detected in seven patients (19%), and none of them had renal impairment requiring hospitalization. We aimed to determine cut-off values for age and dosage for proteinuria development. The analyses revealed that patients who were less than 23 years of age and those treated with deferasirox doses greater than 29 mg/kg/day had higher risk for proteinuria development. Immaturity of renal tubules in younger patients may make them more susceptible to nephrotoxicity [16]. Another obstacle about urinary protein analysis was compliance to test. We found test compliance to be only 75% during the follow-up time. Benefit of monthly urinary protein monitoring of patients, who are on deferasirox treatment, seems controversial. Patients in these two risk groups of younger ages and those who receive higher doses may be followed more strictly than others. Owing to low compliance and self-limited character of proteinuria in patients treated with deferasirox, patients older than 23 years of age, and those treated with doses of less than 29 mg/kg/day may be suggested to be monitored for proteinuria with longer intervals. There is need for further studies in larger sample size; however, our study provides valuable data related to a long follow-up time.

Disclosure statement

No potential conflict of interest was reported by the authors.

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