Original Article *Iran J Ped Hematol Oncol. 2022, Vol 12, No 4, 229-239*

Visual and Auditory Complications during Deferasirox Therapy in Beta-thalassemia

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Received: 02 November 2021 **Accepted:** 14 July 2022

Abstract

Background: Deferasirox is an oral iron chelator widely used to treat iron overload in patients with transfusion-dependent β-thalassemia. This study investigated the prevalence of visual and auditory complications caused by deferasirox.

Materials and Methods: This cross-sectional study included 156 patients aged less than 18 years with transfusion-dependent β-thalassemia and deferasirox iron chelator consumption admitted to the 17 Shahrivar Hospital and the Besat Clinic in Rasht, Iran. All the patients were examined for visual and auditory complications caused by deferasirox in 2019. A checklist of the patients' demographical and clinical data was recorded. Data analysis was done with SPSS and reported by descriptive statistics. Then, Fisher's exact test was performed to examine the association between visual and auditory disorders and the use of deferasirox in terms of disease-related variables including age, sex, age of onset of using chelator, drug use duration, drug dosage, and mean 6-months serum ferritin levels ($P < 0.05$ as the significance level).

Results: Of a total of 156 patients, 103 (66%) were female and 56 (35.9%) were 20-30 years of age. The prevalence of visual acuity change was 0.6%, and the prevalence of sensorineural hearing loss was 1.3%. There was only one female with the visual disorder decreasing to 9/10 and with a dose of 31-40 mg/kg/day with an average of 1000-2500 ng/ml six-month ferritin. Also, two females with hearing impairment were confirmed with a dose of ≤30 mg/kg/day, and an average of ≤1000 ng/ml six-month ferritin. The Fisher's exact test results showed no significant relationship between visual and auditory disorders with the use of deferasirox in terms of disease-related variables ($p>0.05$).

Conclusion: The study's findings showed no significant relationship between visual and auditory disorders with deferasirox consumption. The results indicated the safety of deferasirox regarding visual and auditory side effects. More studies are required to confirm the findings.

Keywords: Beta-thalassemia, Deferasirox, Hearing loss, Iron chelator, Visual acuity

Introduction

Transfusion-dependent β-thalassemia (TDT) is a severe form of β-thalassemia in which patients' lives is dependent on regular blood transfusion. Chronic transfusion therapy causes an iron overload that results in excess non-binding iron entering myocytes, hepatocytes, and endocrine glands. This leads to various complications such as liver disease, endocrine dysfunction, skin hyperpigmentation, and heart problems (1–6).

Among the less studied complications are ophthalmic disorders. Several case reports reported an association between the onset of chelation therapy and occurrence of ocular symptoms (7–9). Also, auditory disorders occur during treatment with these agents for an extended period at high doses and in patients with augmented ferritin levels (7,10,11). Over the last few decades, there have been dramatic developments in survival for patients with thalassemia major due in large measure to enhanced iron chelators. Three types of

[DOI: 10.18502/ijpho.v12i4.10913]

iron chelators are available: deferoxamine, deferasirox, and deferiprone. Due to the limitations of stem cell transplantation, the main treatment option for most patients is supportive therapy in the form of blood transfusion combined with chelator therapy (12). Numerous studies and clinical trials worldwide have shown that each of the three drugs can chelate and remove iron, thereby preventing or alleviating transfusion-related hemosiderosis in thalassemia patients. However, chelators differ significantly in side effect profile, cost, tolerability and ease of compliance, and, to some extent, efficacy per specific patient (13).

In the 1980s, however, some investigators reported ototoxicity and ocular toxicity induced by deferoxamine (7,14,15), although others have suggested that doses less than 50 mg/kg/d are not associated with optic or ocular toxicity. The reported otologic disturbance is bilateral high-frequency sensorineural hearing loss. Nonetheless, a recent meta-analysis showed hearing deficits in nearly one-fourth of pediatric beta-thalassemia patients treated with deferoxamine (16). In addition, hearing loss has also been reported in patients undergoing iron chelation with deferiprone and deferasirox as the most recent oral iron chelators (11). Deferasirox was announced as part of customarily accessible chelators in 2009. Patients with thalassemia major started on deferasirox in case they created unfavorable occasions or were non-compliant to the other chelators. Patients with thalassemia intermedia started on deferasirox in the event that they denied deferoxamine (DFO) or were on hydroxyurea. Side effects are not uncommon with deferasirox. Some studies have shown the side effects of deferasirox on the heart, endocrine organs (thyroid, testes, ovaries, and pancreas), and life (17–22). Iron chelators also can raise serum creatinine and liver enzymes level that should be measured throughout treatment (23). Visual and auditory complications are reported during treatment with these agents for a long time at high doses and in patients with increased ferritin levels. In most cases, the damage was reversible with immediate cessation of the treatment (18,24–27).

Despite high prevalence of deferasirox consumption and numerous studies accessible in the literature, the true scenarios of visual and auditory complications in beta-thalassemia remain fairly inaccurate. In addition, the findings are markedly heterogeneous and inconsistent, with prevalence rates ranging from no visual and auditory disorders to visual and hearing impairment in patients (6,8–10). The present study aimed to monitor visual complications such as color blindness, visual acuity change, cataracts, glaucoma, and retinal disorders, as well as auditory complications such as sensorineural hearing loss, tinnitus, and deafness which are the results of deferasirox consumption.

Materials and Methods

In this retrospective study, 156 transfusion-dependent β-thalassemia patients who had been treated with deferasirox iron chelator for at least one consecutive year were enrolled. The patients were above 10 years and underwent visual and auditory examinations. Eye examinations were performed by an ophthalmologist using a slit lamp (Haag-Streit, Switzerland), an ophthalmoscope (Welch Allyn, USA), Goldmann tonometry (Haag-Streit, Switzerland), an E-chart, and the Ishihara test. Also, auditory disorders were assessed by an ear, nose, and throat (ENT) specialist based on pure-tone audiometry (P.T.A) (MAICO, Germany). A checklist of patient data, including age, sex, age of onset of chelator use, use duration, chelator dosage, and average serum ferritin in the last six months, was recorded during the study. The results of visual examinations, including color blindness, visual acuity change, glaucoma, cataracts,

[DOI: 10.18502/ijpho.v12i4.10913]

retinal disorders, as well as audiometry, any complaint of tinnitus, and hearing loss, were documented in 2019. The data were entered into SPSS.21 statistical software and reported by descriptive statistics. To figure out the relationship between the observed side effects and the use of deferasirox, we performed Fisher's exact test with a significance level of P-value <0.05. Inclusion criteria were age above 10 years, consecutive consumption of deferasirox iron chelator for at least one year, no use of other iron-depleting drugs and combination therapies, and periodic examinations of visual and auditory conditions. Exclusion criteria were the use of drugs with known effects on vision or hearing and vision and auditory problems before starting deferasirox.

Ethical Considration

All the subjects gave their informed consent before participating in the study. The study was approved by the ethical committee for human genome/gene research at the Guilan University of Medical Sciences (IR.GUMS.REC.1399.344).

Results

Data from a total of 156 patients with β-thalassemia using deferasirox were analyzed. Most of the participants were female (103 cases, 66%) and in the age group of 20-30 years (35.9%). The highest percentage (49.4%) of the patients started taking deferasirox at the age of 10-25 years. The duration of deferasirox use in most of the patients was 4-8 years (58.3%). Most of them used this chelator with a dose of 31-40 mg/kg/day, and the highest dose was 40 mg/kg/day. The mean serum ferritin level in the last six months was 1629.16 ± 1183.1 ng/ml, with the highest serum ferritin level being 6419 ng/ml and the lowest serum ferritin level being 230 ng/ml. The highest percentage (44.2%) of the patients had a mean serum ferritin level between 1000 and 2500 ng/ml (Table I). Only one female case with visual impairment was reported as follows: visual acuity decreased to 9/10, in the age group of 10-20 years, with the drug consumption age of 10-25 years, consumption duration of 4-8 years, a dose of 31-40 mg/kg/day with the average of 1000-2500 ng/ml six-month ferritin. There were also two female cases with hearing impairment, both with sensorineural hearing loss problems (impairment in the reception of auditory stimuli or auditory nerve pathway, based on pure-tone audiometry) in the age group of 20-30 years, with drug consumption age of 10-25 years, consumption duration of 4-8 years, a dose of ≤30 mg/kg/day, and the average of ≤1000 ng/ml six-month ferritin. The Fisher's exact test results revealed no statistically significant relationship between the presence of visual disorder in terms of age groups (P = 0.308), sex (P = 0.472), age groups starting deferasirox (P= 0.597) (Table II), drug use duration (P=0.698), drug dose (mg/kg/day) (P=0.397), mean serum ferritin level in the last six months (P = 0.53), and deferasirox use in patients with β-thalassemia (Table III). Also, no statistically significant relationship was found between the presence of auditory disorder in terms of age groups (P = 0.33), sex (P = 0.548), age groups starting deferasirox (P= 0.656) (Table II), drug use duration (P=0.631), drug dose (mg/kg/day) (P=0.172), mean serum ferritin level in the last six months (P = 0.17), and using deferasirox in patients with β-thalassemia (Table III). The t-test results showed no statistically significant difference between the mean values of disease-related variables in patients with β-thalassemia using deferasirox by sex (P> 0.05) (Table IV).

[DOI: 10.18502/ijpho.v12i4.10913]

Table I: Evaluation of demographic characteristics and disease information in patients with β-thalassemia using deferasirox

Variables	Parameters	Number	Percentage
Gender	Male	53	34
	Female	103	66
Age (year) Mean ± SD (min-max)		**25.56±8.9 (10-56)**	
Age	10-20	48	30.8
	20-30	56	35.9
	>30	52	33.3
Age of onset of drug use (year) Mean ± SD (min-max)		**20.43±9.22 (2-49)**	
Age of onset of drug use	≤10	25	16
	10-25	77	49.4
	≥25	54	34.6
Duration of drug use**(year) Mean ± SD (min-max)**		**5.55±2.33 (1-11)**	
Duration of drug use	≤ 4	49	31.4
	4-8	91	58.3
	≥8	16	10.3
Dosage of drug mg/kg/day Mean ± SD (min-max)		**31.11±7.47 (15-40)**	
Dosage of drug mg/kg/day	≤ 30	65	41.7
	31-40	91	58.3
Average of ferritin level in six months (ng/ml) **Mean ± SD (min-max)**		**1629.16±1183.1 (230-6419)**	
Average of ferritin level in six months (ng/ml)	≤ 1000	58	37.2
	1000-2500	69	44.2
	≥2500	29	18.6

[DOI: 10.18502/ijpho.v12i4.10913]

Table II. Frequency distribution of disorders in patients with beta-thalassemia using deferasirox by age, gender, and age of onset of drug use

Variables	Complication		Number	Percentage	Number	Percentage	Number	Percentage	*P* value
			10- 20 years		**20- 30 years**		**>30 years**		
Age	Visual	Yes	1	100	0	0	0	0	0.308
		No	47	30.3	56	36.1	52	33.5	
	Auditory	Yes	0	0	2	100	0	0	0.33
		No	48	31.2	54	35.1	52	33.8	
	Visual or Auditory	Yes	1	33.3	2	66.7	0	0	0.526
		No	47	30.7	54	35.3	52	34	
			≤ 10 years		**10- 25 years**		**>25 years**		
Age of onset of drug use	Visual	Yes	0	0	1	100	0	0	0.597
		No	25	16.1	76	49	54	34.8	
	Auditory	Yes	0	0	2	100	0	0	0.656
		No	25	16.2	75	48.7	54	35.1	
	Visual or Auditory	Yes	0	0	3	100	0	0	0.4
		No	25	16.3	74	48.4	54	35.3	
			Number	**Percentage**	**Number**	**Percentage**			
			Male		**Female**				
Gender	Visual	Yes	0	0	1	100			0. 472
		No	53	34.2	102	65.8			
	Auditory	Yes	0	0	2	100			0. 548
		No	53	34.4	101	65.6			
	Visual or Auditory	Yes	0	0	3	100			0. 551
		No	53	34.6	100	65.4			

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Table III. Frequency distribution of disorders in patients with beta-thalassemia using deferasirox by drug use duration, drug dosage, and average ferritin level in six months

Variables	Complication		Number	Percentage	Number	Percentage	Number	Percentage	*P* value
			≤ 4 years		**4-8 years**		**> 8 years**		
Duration of drug use	Visual	Yes	0	0	1	100	0	0	0.698
		No	49	31.6	90	58.1	16	10.3	
	Auditory	Yes	0	0	2	100	0	0	0.631
		No	49	31.8	89	57.8	16	10.4	
	Visual or Auditory	Yes	0	0	3	100	0	0	0.677
		No	49	32	88	57.5	16	10.5	
			≤ 30		**31- 40**		**Total**		
Dosage of drug mg/kg/day	Visual	Yes	0	0	1	100	1	100	0.397
		No	65	41.9	90	58.1	155	100	
	Auditory	Yes	2	100	0	0	2	100	0.172
		No	63	40.9	91	59.1	154	100	
	Visual or Auditory	Yes	2	66.7	1	33.3	3	100	0.571
		No	63	41.2	90	58.8	153	100	
			≤ 1000		**1000- 2500**		**>2500**		
Average of ferritin level in six months ng/ml	Visual	Yes	0	0	1	100	0	0	0.53
		No	58	37.4	68	43.9	29	18.7	
	Auditory	Yes	2	100	0	0	0	0	0.17
		No	56	36.4	69	44.8	29	18.8	
	Visual or Auditory	Yes	2	66.7	1	33.3	0	0	0.594
		No	56	36.6	68	44.4	29	19	

[DOI: 10.18502/ijpho.v12i4.10913]

Table IV. Comparison of different amounts of disease-related factors in patients with β-thalassemia using deferasirox regarding sex

Variable	Gender	Number	Mean ± SD	*P* value
Age	Male	53	26.16±8.91	0.544
	Female	103	25.25±8.92	
Age of onset of drug use (years)	Male	53	21.35±9.14	0.372
	Female	103	19.96±9.27	
Duration of drug use (years)	Male	53	5.35±2.11	0.447
	Female	103	5.66±2.44	
Average of ferritin level in six months (ng/ml)	Male	53	1765.1±1371	0.305
	Female	103	1559.19±1073	
Dosage of drug (mg/kg/day)	Male	53	32.28±6.97	0.162
	Female	103	30.51±7.6	

Discussion

Iron chelation therapy is a permanent requirement for transfusion-dependent patients with β-thalassemia. However, regular transfusion and iron overload can lead to multi-organ damage (19,20). The use rate of oral chelators is growing because of compliance issues for deferoxamine. A limited amount of comparative studies observed specific advantages and disadvantages of oral chelators. As mentioned in studies, visual and auditory side effects of deferasirox are rare. However, hearing loss has been stated in patients undertaking iron chelation with deferiprone and deferasirox (11). Bhardwaj et al. studied 30 thalassemic patients undergoing regular iron chelation therapy with DFO and deferasirox between January 1, 2010, and June 30, 2010. After 12 months of chelation therapy, they observed a high rate of ototoxicity in patients by using distortion product otoacoustic emissions (DPOAEs) (46%). Previous studies had shown a correlation between ototoxicity and dose, duration, or therapeutic index of chelation therapy. However, no variables that could reliably predict ototoxicity were identified (28). In a case study by Pan et al., a 17-year-old boy with β-thalassemia treated with oral deferasirox developed bilateral painless visual disorder, central scotoma, and dyschromatopsia. Fluorescein angiography and electroretinography were normal. This was the first recorded case of deferasirox-induced maculopathy and related changes in optical coherence tomography (OCT). Stopping the drug and then taking it at a lower dose led to improved vision and field of vision in the patient (27). Therefore, we studied the prevalence of visual impairment such as color blindness, visual acuity change, cataracts, glaucoma, and retinal disorders, as well as sensorineural hearing loss, tinnitus, and deafness from deferasirox. We also examined their association with the variables in the population. In this study, all patients with transfusion-dependent β-thalassemia were taking deferasirox. Only one case of visual acuity changes with a visual acuity of 9/10 in the right eye was found. However, this reduction in visual acuity is not a visual disorder by itself, and there was no evidence of deferasirox complications in the retina on ophthalmoscopic examination of the patient's eye. Even so, the retinal

[DOI: 10.18502/ijpho.v12i4.10913]

examination is unreliable in the absence of OCT. The prevalence of visual acuity change in this study population was 0.6%. Different results in our study may be due to differences in the number and type of studied people, drug use duration, and deferasirox dose. In another study, a case of deferasirox-related retinopathy was reported in a 17-year-old girl with a history of sickle cell anemia who underwent simultaneous blood transfusion and iron chelator therapy. After discontinuation of deferasirox, visual acuity and electrophysiological responses improved. Decreased vision in the patient was associated with a lack of electrophysiological responses in the absence of anatomical or vascular disorders and the overall use of deferasirox. No previous case of retinopathy associated with deferasirox was reported. It was stated that oral deferasirox caused reversible retinopathy in this patient, and physicians should be aware of it (29). Another case was a 14-year-old boy with repeated beta transfusions thalassemia from childhood, after a high dose of deferasirox manifested by the sudden loss of vision. Clinical and physical findings were consistent with deferasirox-induced optic neuritis. Recovery was obtained after partially stopping deferasirox. This is the rarest complication, and caution should be exercised in patients who have been using deferasirox for extended periods (24). A prospective cohort study indicated that none of 80 patients, containing 18 children and 62 adults, demonstrated non-correctable changes in visual acuity. It is concluded that chelating therapy (with subcutaneous deferoxamine, oral deferiprone, or deferasirox) is safe for retina and optic nerve function. Correspondingly, it has been demonstrated that iron chelation therapy was not related to fundus changes; instead, a higher dose of deferasirox may even have a protective influence on the fundus oculi (7% per mg/kg/day). The reasons for this possible protective effect are currently unknown. Thus, this feature needs to be examined with further studies (8).

It was also observed that deferasirox was associated with developed sensorineural hearing loss that was significantly related to the dose and duration of drug use (25). A total of two cases of hearing impairment were found in our study: one was mild sensorineural hearing loss in the left ear, and the other was mild bilateral sensorineural hearing loss, accounting for 1.3% of the total. In a study on the incidence of autotoxicity in children of transfusion-dependent thalassemia, no hearing loss associated with deferasirox was reported in the population (30). Vichinsky et al. examined the long-term safety and efficacy of deferasirox in young children with transfusion-induced hemosiderosis during 5 years of observation. Overall, the safety and efficacy of deferasirox in young children in a long-term observational study were reliable with the known profile of this drug, which may be consistent with the present study (4).

Nonetheless, Osma et al. (2015) conducted a study on sensorineural hearing loss in 159 patients with beta-thalassemia aged 5 to 61 years (69 men and 90 women) treated with deferasirox, deferoxamine, deferiprone, and a combination of deferoxamine and deferiprone for at least one year, including one year before the study using the descriptive cross-sectional method to compare the performance of the DPOAE test (Distortion product otoacoustic emissions) and PTA (pure tone audiometry) as audiological monitoring methods. The results showed no significant difference between the ability of DPOA and PTA testing to detect autotoxicity. In a study, it was observed that deferasirox and deferiprone were associated with autotoxicity in patients with beta-thalassemia (26).

Also, Khan et al. (2019) studied sensorineural hearing loss and its association with the duration of chelator

[DOI: 10.18502/ijpho.v12i4.10913]

treatment in patients with beta-thalassemia. They examined 198 patients with beta-thalassemia aged between 5-25 years. In their study, half of the patients developed sensorineural hearing loss after using deferasirox, which contradicts our results. It was shown that sensorineural hearing loss was significantly related to the dose and duration of drug use (25). Due to the importance of early detection of these complications, many of which are reversible in the early stages or can be prevented from worsening, it is recommended to perform visual and auditory examinations at least annually to control side effects in patients taking deferasirox.

Despite the high number of patients with transfusion-dependent β-thalassemia at the 17 Shahrivar Hospital and Besat Clinic, a large number of patients did not have the documented follow-up for regular visual and auditory examinations. Another noteworthy point is that methods, such as OCT, electroretinography, the field of view, and color vision disorders, are currently used for accurate examination of visual complications. However, these methods were not used to evaluate all patients in this retrospective study.

Conclusion

No significant association was observed between visual and auditory disorders with deferasirox consumption. The present study's results are consistent with the results of some studies in the field and show the safety of deferasirox regarding visual and auditory complications. Future longitudinal studies of the patients, treatment, and visual and hearing impairments are recommended to identify the pathogenesis and prevalence of deferasirox-related disorders in beta-thalassemia and manage the side effects.

Acknowledgments

We would like to thank all hospital staff and specialists for their assistance in recording cases. The study design was approved by the Ethical Committee of the Guilan University of Medical Sciences [IR.GUMS.REC.1399.344]. The authors declare no competing interests. The study was self-funded.

Conflict of interest

The authors declare no conflict of interest.

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[DOI: 10.18502/ijpho.v12i4.10913]