

Deferasirox adherence in patients with thalassemia: Exploring the association with patient knowledge and ferritin levels

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Received 25 May 2024 ♦ Accepted 10 July 2024 ♦ Published 30 July 2024

Citation: Shaker RA, Abduljabbar Rizij F, Jasim TA (2024) Deferasirox adherence in patients with thalassemia: Exploring the association with patient knowledge and ferritin levels. *Pharmacia* 71: 1–6. <https://doi.org/10.3897/pharmacia.71.e128144>

Abstract

In this study, data from 171 patients with thalassemia were analyzed. There was high variability in ferritin levels among patients, with a median of 2290 ng/mL. The median Morisky adherence score was 4, and 75% of the patients had low adherence levels to deferasirox. There were no significant correlations between the adherence score and patients' sociodemographic data. However, a significant positive correlation was noted between the adherence score and the knowledge score of the patients. Ferritin levels were significantly and negatively correlated with the adherence score, as demonstrated by the highest ferritin level observed among patients with low levels of adherence. In conclusion, a low level of adherence to deferasirox was noted among patients with thalassemia. Adherence levels were directly associated with patients' knowledge of the disease and its therapy, while ferritin levels were inversely linked to adherence levels. Thus, tailored and effective strategies are needed to optimize chelation therapy and patient outcomes.

Keywords

thalassemia, deferasirox, knowledge, adherence, serum ferritin

Introduction

Thalassemia is one of the most common inherited hematological disorders worldwide, with approximately 5.0% of the global population carrying alpha-thalassemia and 1.5% carrying beta-thalassemia (Man et al. 2019; Eziefula et al. 2022). Thalassemia has become a significant public health burden and represents a major cause of human suffering, specifically for those patients with a severe form of the disease (Piel and Weatherall 2014; Piel 2016; Benz and Sankaran 2023). Over the past 50 years, life expectancy for thalassemic patients has changed dramatically, especially for the severe type, shifting

from childhood lethal disease to adulthood stage disease with improved outcomes due to the use of several strategies, including intensified transfusion regimens and Iron Chelation Therapy (ICT) (Chonat and Quinn 2017). The mainstay of therapy is long-life blood transfusion and chronic use of ICT (Lee et al. 2009; Belhoul et al. 2013; Dimitriou et al. 2022). Removal of excess iron and prevention of its accumulation by chelation therapy constitute the critical strategy to reduce morbidity, improve quality of life, and expand the life expectancy of patients (Reddy et al. 2022). Furthermore, life expectancy largely depends on compliance with the prescribed treatments, where about 67% of patients are

predicted to survive through the age of 50 with at least one complication, and from those, about 33% are predicted to survive without any disease-related complication (Weidlich et al. 2016; Farmakis et al. 2020).

Oral ICT has become accessible to patients over the last two decades, including deferiprone, administered three times daily, and deferasirox, administered once daily (Saliba et al. 2015; Mohamed et al. 2022). These ICT agents have been found to be effective in removing excess iron and achieving good therapeutic outcomes, but they require careful monitoring and good adherence to the dosage regimen (Bahnasawy et al. 2017; Eziefula et al. 2022; Lee et al. 2024). Unfortunately, more than half of the patients pass away before the age of 35, mostly due to poor adherence to the ICT (Saliba et al. 2015). Previous research has indicated that the adverse reactions, along with the difficulties of administering deferoxamine parenterally and the frequency of administering deferiprone and deferasirox, result in a worse adherence to iron chelation regimens, which in turn leads to weaker control over the deposition of iron in critical organs (Delea et al. 2007; Wahidiyat et al. 2018). Non-adherence negatively impacts treatment effectiveness, hence causing the patients to face unnecessary complications, worsening medical conditions, and resulting in higher morbidity and mortality rates (Eziefula et al. 2022). In a recent meta-analysis study, a wide range of adherence rates to different ICTs was reported, varying from the lowest 57% to the highest 88% (Reddy et al. 2022).

Deferasirox is the most commonly used oral chelation therapy among Iraqi patients because of its ease of use and free-of-charge provision by the Iraqi Ministry of Health to all thalassemia centers. However, a cohort study reported higher median serum ferritin levels, more prominent thalassemia complications, and a lower median age among Iraqi patients with beta-thalassemia compared to other countries, indicating the suboptimal management of thalassemia and the need to optimize chelation therapy (Sadullah et al. 2020). Therefore, this study was designed to determine the adherence level of thalassemic patients to deferasirox and explore its association with patients' variables, in addition to observing the impact of adherence on serum ferritin level.

Subjects and methods

A cross-sectional, observational study was conducted in the specialized center for thalassemia at Al Zahraa Teaching Hospital in Al Najaf Governorate, Iraq, from February to October 2023. The eligible patients for this study were male and female patients previously diagnosed with thalassemia, visiting the center constantly, and taking deferasirox for the last 6 months. During the study interval, we approached 194 patients who were administered ICT, and about 177 patients met the eligibility criteria; we sought their permission for involvement in this study after fully explaining to them the research objectives. The patient information was collected using a revised questionnaire adapted from previous literature (Lee et al. 2009; Alam

et al. 2022). The first part of the questionnaire included patients' sociodemographic data, clinical information, and treatments. The second section involved evaluating patients' knowledge regarding the disease through ten questions focusing on disease information, its hereditary nature, main treatments, the source of iron overload and its impact on different organs, and finally, awareness about iron chelation therapy and its administration; these knowledge questions were to be answered with "yes," "no," or "I don't know" responses. One mark was given to the response "yes," while a zero mark was given to the responses "no" and "I don't know" (Majid et al. 2021; Wahidiyat et al. 2021; Fakhreldain and Assad 2022). The adherence level of patients to deferasirox was assessed using the 8-item Morisky Medication Adherence Scale (MMAS-8) (entitlement certificate no. 1014-9003-3176-6273-1395, 2023). It consists of 8 questions with "yes" or "no" responses for the first seven items, involving one mark for a "no" response and a zero mark for a "yes" response; however, for the fifth item, the marks are reversed. The eighth item's response is graded on a 5-point Likert scale. The sum of the responses of all items and the 3-category Likert scale is then used to evaluate the adherence level, with <6 = low adherence, 6-8 = medium adherence, and 8 = high adherence. The last part of the questionnaire included the most important laboratory data of the patients, such as serum ferritin, hematocrit (HCT), hemoglobin (HB), alanine aminotransferase (ALT), aspartate transaminase (AST), urea, and creatinine (CR). All this information was collected through face-to-face interviews and from the clinical records of eligible patients themselves or their parents for those under 12 years old. The participants were assured that their names and other contact information would be kept confidential. This study protocol and questionnaires were approved by the scientific committee of research at Najaf Health Directorate (registration no. 5340/Feb 2, 2023), the ethical committee for clinical studies at Kufa Faculty of Medicine, University of Kufa (MEC-40/2023), and the ethics and scientific committee at the Faculty of Pharmacy, Kufa University (5318 on 29 December 2022); additionally, this study has been registered at ClinicalTrials.gov (identifier no.: NCT06210139). The data underpinning the analysis reported in this paper are deposited at the "Data Repository" of Zenodo at <https://zenodo.org/records/12730731#:~:text=DOI%2010.5281/zenodo.12730730>.

Statistical analysis

The data were analyzed using the statistical package for the social sciences (SPSS) software version 25. Descriptive statistics were obtained for all study items. Continuous variables have been expressed as mean \pm SD and median with interquartile range (IQR), whereas categorical variables have been expressed as frequency and percentage. The Shapiro-Wilk test was used to assess the normality of the distribution of parameters. Mann-Whitney and Kruskal-Wallis tests were used to assess the effect of the difference in Morisky adherence scores on patient variables. Spearman's Rho correlation was used to measure the re-

relationship among patients' knowledge, adherence scores, and serum ferritin levels. A P-value of less than 0.05 was considered statistically significant.

Results

In the initial survey, 194 patients were taking ICT, and out of them, 177 patients were taking deferasirox. From these people, 174 patients completed the Morisky adherence survey. To ensure the strength of the statistical analysis, we carefully screened the data for outliers. After the removal of three outliers from the data, we conducted statistical analysis on the remaining 171 patients' data.

Male and female distributions were found to be equal among the patients. Most of the patients lived in urban areas (64.9%), about 63% had primary or secondary education, and around 75% of the patients were unemployed. Most of the patients employed stated having a low to moderate income. However, all of them received blood transfusions, as shown in Table 1. There was high variability in serum ferritin levels among patients, with a median of 2290.5 ng/mL, and 25% of patients had values below 1023.5 ng/mL, while 75% of patients had values below 3733.7 ng/mL. The average hemoglobin level of the patients was 7.76 (± 1.3). In Table 2, the knowledge average score was 7.4 (± 1.88) out of 10. The median Morisky score of adherence was 4, 25% of patients had an adherence score below 2, and 75% of patients had a value below 6.

Fig. 1 shows that about three-quarters (75%) of the participants had low adherence to oral ICT deferasirox, and only 6% exhibited a high adherence level. The MMAS-8 results showed more than half of the patients (58%) to usually forget to take their medicines; about more than half of the participants (59.6%) reported that they did not take their medicines on some days of the previous two weeks, indicating non-adherence issues to extend beyond mere forgetfulness. Additionally, about 50.9% of patients reported that they stopped taking deferasirox without telling their doctor because they felt worse. Additionally, more than a quarter of the patients (27.5%) confirmed that they did not take deferasirox the day before, and a third of them reported that they stop taking medicine whenever they feel that their symptoms are under

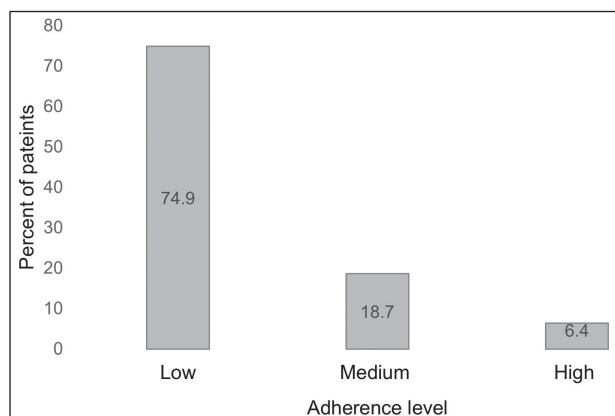


Figure 1. The adherence levels of the patients according to the Morisky adherence score.

control. Considerably, more than two-thirds of thalassemia patients (78.9%) in the survey showed that adhering to their daily deferasirox regimen is a hassle. Only 37.4% of patients answered that they never had any difficulty remembering to take all their medicine, as presented in Table 3.

No significant correlations were observed in Table 4 between the total Morisky score of adherence and all patients' sociodemographic characteristics, including age, gender, occupation, education level, and monthly income.

Table 1. The sociodemographic characteristics of the participating patients.

Patients' variables	Frequency	Percent
Gender		
Male	86	50.3%
Female	85	49.7%
Age		
Adult	126	26.3%
Child	45	73.7%
Area of residence		
Rural	60	35.1%
Urban	111	64.9%
Level of education		
No formal education	47	27.5%
Primary or Secondary	107	62.6%
College or higher	17	9.9%
Occupation		
Not employed	128	74.9%
Governmental employed	36	21.1%
Healthcare provider	7	4.1%
Monthly income		
Low	75	43.9%
Moderate	94	55.0%
Higher	2	1.2%
Frequency of transfusion		
Once monthly	49	28.7%
Twice monthly	92	53.8%
Thrice monthly	30	17.5%
Consanguineous marriage		
Yes	139	81.3%
No	32	18.7%
Treatments		
Deferasirox	174	100%
Desferal	43	25.1%
Folic acid	160	93.6%
Calcium	83	48.5%
One alpha	89	52.0%

Table 2. The parameters of the participating patients.

Parameter	N	Mean	SD	Median	25% (IQR)	75% (IQR)
Age (years)	171	18.05	9.56	16	11	20
Weight (kg)	171	38.79	14.35	40	25	50
Serum ferritin (ng/mL)	171	2734	2139	2290	1023	3733
HCT (%)	169	23.64	3.65	24	21.45	26
HB (g/L)	169	7.69	1.30	7.73	6.91	8.61
ALT (U/L)	169	26.6	28.6	16.7	7.8	34.0
AST (U/L)	169	44.6	30.9	36.1	25.0	52.6
UREA (mg/dl)	169	25.5	8.4	24.9	19.6	32.4
CR (mg/dl)	169	0.41	0.15	0.39	0.30	0.50
Total knowledge score	171	7.4	1.9	8	6	9
Total Morisky score	171	4.2	2.2	4	2	6

Table 3. The answers of the patients to the eight Morisky adherence items.

Morisky adherence items	Yes, N (%)	No, N (%)
1 Do you sometimes forget to take your medicine?	113 (58)	58 (33.9)
2 People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine	102 (59.6)	69 (40.4)
3 Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?	87 (50.9)	84 (49.1)
4 When you travel or leave home, do you sometimes forget to bring along your medicine?	62 (36.3)	109 (63.7)
5 Did you take all your medicines yesterday?	124 (72.5)	47 (27.5)
6 When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	53 (31.0)	118 (69.0)
7 Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	135 (78.9)	36 (21.1)
8 How often do you have difficulty remembering to take all your medicine?	Never/Rarely Once in a while Sometimes Usually All the time	64 (37.4) 44 (25.7) 35 (20.5) 20 (11.7) 8 (4.6)

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Table 4. The correlation of the total Morisky score with the patients' characters.

Patients' characters	N	Morisky score		Mean Rank	P-value
		Mean of	SD		
Female	86	4.15	2.34	85.9	0.685
Male	85	4.30	2.19	89.0	
Child	45	4.089	2.4	86.9	0.927
Adult	126	4.27	2.2	87.7	
Rural	60	3.77	1.93	77.9	0.104
Urban	111	4.46	2.3	92.7	
No formal education	47	3.61	1.88	73.9	0.078
Primary or Secondary	107	4.51	2.34	94.2	
College or higher	17	4.02	2.23	82.7	
Low income	75	4.09	2.36	85.1	0.516
Moderate income	94	4.35	2.2	90.1	
High income	2	3.00	1.4	54.5	
Not employed	128	4.05	2.22	83.5	0.145
Employed	36	4.67	2.06	97.1	
Health care provider	7	5.14	2.44	111.6	
Mono ICT	128	4.42	2.1	86.1	0.523
Combination ICT	43	4.15	2.3	91.6	

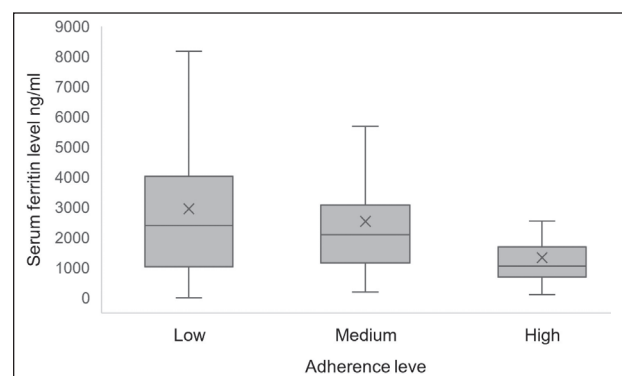
Significant (P-value <0.05) according to Mann-Whitney test and Kruskal-Wallis test.

Interestingly, there were significant positive correlations noted between the total scores of patients' knowledge and medication adherence scores. Serum ferritin levels exhibited a significant negative correlation with the total scores of medication adherence. In other words, with an increase in medication adherence, there was a decrease in serum ferritin levels, as presented in Table 5. More specifically, in Fig. 2, the patients with low medication adherence had the highest serum ferritin level compared to the high level of adherence category.

Table 5. The correlations among adherence, knowledge, and serum ferritin.

Correlated parameters	N	Correlation r	P value
Adherence score and knowledge	171	0.232	0.003
Ferritin level and Adherence	171	-0.208	0.006
Ferritin level and Knowledge	171	-0.046	0.550

Correlation is significant at the 0.05 level.

**Figure 2.** Pairwise comparisons of ferritin levels according to adherence categories using the Kruskal-Wallis test.

Discussion

According to the results of the current study, 75% of the patients demonstrated poor adherence to oral ICT, namely deferasirox, as shown in Fig. 1. This is consistent with the findings from a study conducted on 50 Egyptian patients treated with deferasirox, which reported a low adherence rate of 86% (Aboeela et al. 2018). In addition, another cross-sectional study revealed that just 51.7% of patients had good adherence to ICT, indicating a suboptimal degree of adherence (Mohamed et al. 2022). Furthermore, the findings of a meta-analysis study of 15 articles showed inconsistent adherence rates to various ICT regimens among thalassemic patients. The studies included in the meta-analysis applied different methods to assess adherence, such as patient interviews, pill counting, and self-assessments. It has been found to be very challenging to achieve good and sustained adherence to ion chelators (Theppornpitak et al. 2021). Many reasons have been observed to contribute to poor adherence, such as forgetfulness, inconvenience, treatment beliefs, and knowledge level (Sidhu et al. 2021; Mohamed et al. 2022). The high rate of non-adherence in the current study can be attributed to the requirement that deferasirox be taken in the morning on an empty stomach and dispersed in water; patients may view this as a challenging practice, which could

negatively impact their compliance (Sidhu et al. 2021). In addition, most of the patients in our study reported that they usually stopped taking deferasirox because they had gastrointestinal side effects or felt uncomfortable, which raised the non-adherence rate even further.

Knowledge and awareness about the disease and its treatment are fundamental to ensuring good treatment adherence in different disease conditions (Remien et al. 2003; Aydinok et al. 2005; Lee et al. 2009). The current study has revealed adherence to be significantly correlated with patients' knowledge about the disease and chelation therapy; in other words, patients who had an extensive understanding of thalassemia and its therapy were associated with good adherence to the ICT. This positive correlation between the knowledge score and patient adherence level has also been reported in several studies (Lee et al. 2009; Al-Kloub et al. 2014; Mohamed et al. 2022; Shaker et al. 2024). Insufficient knowledge about the disease and its treatment may negatively affect attitudes and behaviors toward treatment adherence and consequently be associated with poor adherence (Amico et al. 2005; Lee et al. 2009).

Poor adherence to chelation therapy has been found to result in inadequate removal of iron, thus leading to an increase in serum ferritin levels. The present study showed serum ferritin levels to be inversely correlated with the rate of adherence. We observed lower serum ferritin levels among patients with high adherence scores compared to patients with low adherence scores, as shown in Fig. 2. Similarly, negative associations between patients' ferritin levels and treatment adherence were noted in a previous study (Lee et al. 2009). As well, a recent multicenter cross-sectional study showed a statistical correlation between serum ferritin level and adherence score, and further, a sub-analysis of the study group also revealed a significant correlation between serum ferritin level and forgetfulness or inconvenience (Mohamed et al. 2022).

Moreover, the association between non-compliance with ICT and high serum ferritin levels was described in a Malaysian cross-sectional study, which stated serum ferritin levels to be greater than 1000 ug/L in two-thirds of the non-compliant patients (Chat Chai et al. 2021). Non-adherence may impact the effectiveness of iron chelators, resulting in iron overload and its accumulation in the liver and heart of the patients, thus increasing the patients' morbidity and mortality (Chat Chai et al. 2021; Sidhu et al. 2021). Good adherence to chelation therapy is critical to preventing iron overload and its complications. Also, optimum adherence to ICT, such as deferasirox, may improve the patients' health-related quality of life and survival rate, thus ensuring the longevity of thalassemic patients (Huang et al. 2015; Mohamed et al. 2022). Generally, ensuring disease knowledge and an understanding of its treatments are essential factors influencing adherence (Remien et al. 2003; Amico et al. 2005; Aydinok et al. 2005; Lee et al. 2009); patients should receive accurate and comprehensive information from healthcare providers about the disease, its therapy, and how to manage side effects. They should also be reminded about the importance of well-adhering to ICT in order to ensure treatment effectiveness and optimum therapeutic outcomes.

Conclusion

This study has revealed poor adherence levels to deferasirox in thalassemic patients and, hence, high serum ferritin levels in non-adherence patients. Interestingly, adherence score has been directly correlated with the knowledge level of patients, and ferritin level is inversely correlated with adherence score. Thus, further research is needed to develop a directed interventional program to improve adherence to this treatment and ensure proper treatment outcomes.

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