



Reduction of Liver Iron Load in Adult Patients with β -Thalassemia Major Treated with Modern Chelation Modalities

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Abstract

Background: Management of beta-thalassemia major (TM) requires life-long hemotransfusions leading to iron overload. Iron elimination is enhanced by the use of modern chelators.

Aim: To assess the effect of modern chelation therapy by dynamics of serum ferritin concentration and liver MRI T2*.

Patients and methods: Forty-six patients with TM (male to female ratio = 1:1, mean age 33.2±10.9 years) were prospectively studied between 2011 and 2014. Twenty-one patients (45.7%) were treated with deferasirox, 17 (37%) – with deferiprone, and 8 (17.3%) – with deferiprone in combination with deferoxamine. Ferritin was measured by ELISA. MRI T2* was assessed by Siemens Magnetom Avanto 1.5T. The patients were allocated into 3 groups based on their initial ferritin level and liver MRI T2*. Statistical analysis was performed using SPSS v. 18 for Windows. Data were analysed by descriptive analysis, analysis of variance and correlative analysis, means were compared using t-test and one-way ANOVA.

Results: In 2011, 9 (19.5%) patients had normal liver MRI T2*; in 2014 they were 17 (37%). The patients with mild grade liver siderosis were 12 (26%) in 2011, and in 2014 they were 14 (30.4%). In 2011, the patients with moderate liver siderosis were 14 (30.4%), and in 2014 – 12 (26.0%). Eleven patients (23.9%) had severe liver siderosis in 2011 and only two patients (4.0%) were diagnosed with the condition in 2014.

Conclusion: A reduction of iron overload was found in all studied groups. This positive effect is attributed to the use of modern chelators and the ease of access to accurate monitoring.

Keywords

beta-thalassemia major, hepatic iron overload, ferritin, MRI T2*

INTRODUCTION

Beta-thalassemia major (TM) is a hereditary hemolytic anemia in which regular blood transfusions are the mainstay of care. However, it causes iron-overload (IO) that

requires monitoring and management by long-term iron chelation therapy to prevent cell death and organic dysfunctions which can be fatal.¹ The annual quantity of IO amounts to 7-14 g.² Initially, iron accumulates in the reticuloendothelial system of bone marrow, spleen and liver,

followed by accumulation in hepatocytes, cardiomyocytes and parenchymal cells of endocrine glands.³ The concentration of iron ions in the organism leads to organ damage by different mechanisms, thus it is a negative prognostic and survival limiting factor in patients with TM.⁴ Iron metabolism in the affected cells is extremely decreased. To enhance it, clinicians rely on iron-chelating agents.⁵ Although adequate oral iron chelation therapy is promising for the treatment of transfusional iron-overload, some patients are less compliant with it, and others suffer from long-term effects of iron overload. Different indicators capable of assessing the total IO in the body are used to monitor the effect of iron chelating agents. Ferritin is the major binding protein in the body's iron stores. It is found predominantly in the liver, spleen, and in small amounts in the serum.^{6,7} The availability of serum ferritin is a reason for its routine use in total IO assessment by most treatment centers. The method lacks specificity in cases of elevation of serum ferritin concentration because of inflammation, vitamin C intake or after allogeneic hematopoietic stem-cell transplantation.^{8,9} In such cases liver iron concentration, measured by MRI ^{*}T2 is particularly useful.¹⁰ Most of the studies have found a very good correlation between serum ferritin concentrations and liver iron load measured by MRI^{*}T2 and recommended both of the methods for routine IO monitoring.^{10,11} Liver is the major iron storage in the body, containing approximately 70% of the total body iron. It is known that the liver iron concentration correlates with the total body IO in patients with transfusion-dependent anemia.¹² This the reason why liver iron load assessment is of extreme importance for TM patients. Traditionally, the assessment of liver iron was performed by liver biopsy – an invasive method that is not tolerated well by all patients.¹³ Nowadays liver IO is tested by MRI T2*. The method measures iron in milligrams per gram of dry liver tissue and estimates the risk of organ damage. Liver iron concentrations higher than 1.6 mg/g of dry tissue are considered high. Values of less than 7 mg/g are associated with low risk for complications and those between 7 and 15 mg/g – with intermediate risk. Patients with 15 mg/g are proven to have serious risk of liver damage – such as fibrosis and cirrhosis. Current advances of modern chelation therapy have led to better compliance of patients with TM, less complications and higher overall and event – free survival due to more adequate elimination of IO.¹⁴

The aim of this study was to analyze the dynamics of liver IO assessed by serum ferritin concentration and MRI T2* in TM patients treated by deferasirox (DFX), deferiprone (DFP) or deferiprone (DFP) + deferoxamine (DFA) combination therapy.

PATIENTS AND METHODS

Our analysis comprised 46 TM patients followed-up in the Hematology Department of St George University Hospital in Plovdiv, Bulgaria between 2011 and 2014. All patients

were on regular transfusion therapy started early in their childhood. DFX, DFP, DFP+DFA were used as chelation therapy in the three study groups. The values of serum ferritin, and MIR T2* were used for assessment of IO. According to ferritin levels the patients were allocated into the following groups: ferritin <1000 µg/ml, ferritin between 1000 and 2500 µg/ml, and ferritin > 2500 µg/ml. According to the MIR T2* values patients were allocated as follows: patients with normal liver iron load >6.3 ms (corresponding to < 2 mg/g of dry weight); mild liver IO 2.7-6.3 ms (corresponding to 2-5 mg/g of dry weight); moderate liver IO 1.4 – 2.7 ms (corresponding to 5-10 mg/g of dry weight); severe liver IO < 1.4 ms (corresponding to >10 mg/g of dry weight). Ferritin was measured using ELISA. MRI T2* was assessed by Siemens Magnetom Avanto 1.5T. Statistics were performed by descriptive statistics, analysis of variance, and correlative analysis, means were compared using one-sample t-test and one-way ANOVA (SPSS v. 18 for Windows).

RESULTS

Demographic distribution within the cohort was 23 males and 23 females (1:1) (mean age 33.2±10.9 years). Respective of treatment modality three groups were formed: group 1 consisted of 8 patients (17.3%) (mean age 28.63±12.85 years, males to females ratio 5:3) who received DFA + DFP, group 2 were on DFX – 21 patients (45.7%) (mean age 32.14±10.32 years, males to females ratio 8:13), and group 3 were on DFP – 17 patients (37%) (mean age 31.82±10.25 years, males to females ratio 10:7). No significant difference was found in the age and sex distribution between the groups (**Fig. 1**).

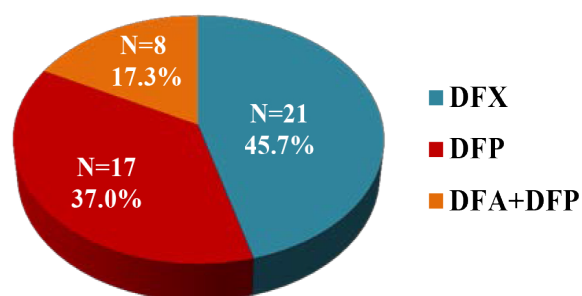


Figure 1. Distribution of patients by modality of treatment.

Over a four-year period (2011-2014), the patients receiving modern chelating agents showed a significant reduction in their IO measured by serum ferritin concentrations. The proportion of patients with ferritin < 1000 µg/ml increased from 43.5% (20 patients) in 2011 to 65.2% (30 patients) in 2014 ($p=0.029$) while the proportion of patients with ferritin > 2500 µg/ml decreased from 23.9% (11) to 6.2% (3) ($p=0.033$). The distribution in groups according to ferritin level in two time points in 2011 and 2014 is shown in **Figs 2A, 2B**. Improvement in IO after chelating was also

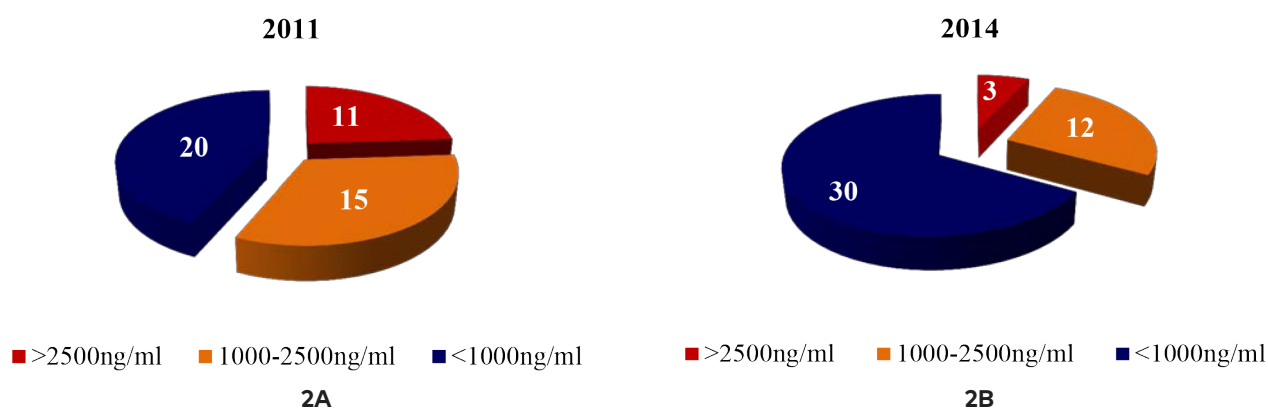


Figure 2. Distribution of patients by ferritin level in 2011 (A) and in 2014 (B).

registered when measuring liver iron concentration by MRI T2*. In 2011, 9 (10.2%) patients had normal levels of liver iron concentration, while in 2014 their number went up to 17 (37.0%) ($p=0.045$). The number of patients with mild grade of liver IO in 2011 and 2014 was 12 (26.0%) and 14 (30.4%), respectively (NS). In 2011, the patients with moderate liver IO were 14 (30.4%), in 2014 – 12 (26.0%), NS. The group with severe IO in 2011 numbered 11 (23.9%) patients, while after treatment their number decreased to 2 (4.3%) patients in 2014 ($p=0.041$) (Figs 2A, 2B, 3).

Comparing the dynamics of serum ferritin levels at baseline and in 2014, a significant reduction was found in all three therapeutic regimens. Most expressed improvement was registered for the patients treated with DFP. (Table 1)

The beneficial dynamics in ferritin serum levels after iron-chelation therapy corresponds to the data of liver IO from MRI T2*. In all three therapeutic modalities there is a significant increase of MRI T2* in 2014 compared to 2011 ($p=0.045$). This improvement is the greatest in the

DFP-treated patients but the difference between the three treatment modalities failed to reach statistical significance (Fig. 3).

DISCUSSION

The presented data are the first single center results reported from Bulgaria. Our analysis comprises a relatively young patient's cohort (mean age 33.2 ± 10.9 years) that was regularly chelated since their childhood years with the only available agent at that time – DFA. The allocation to treatment modalities was implemented according to the baseline results of ferritin serum levels and MRI T2* of liver and myocardium. By the time of the initiation of modern chelation therapy¹⁵ that corresponds to the first period of our study (2011). 56.6% of the patients had ferritin level above 1000 $\mu\text{g/ml}$, 54% had moderate to severe liver siderosis assessed by MRI T2*. In a period of 4 years (up to 2014)

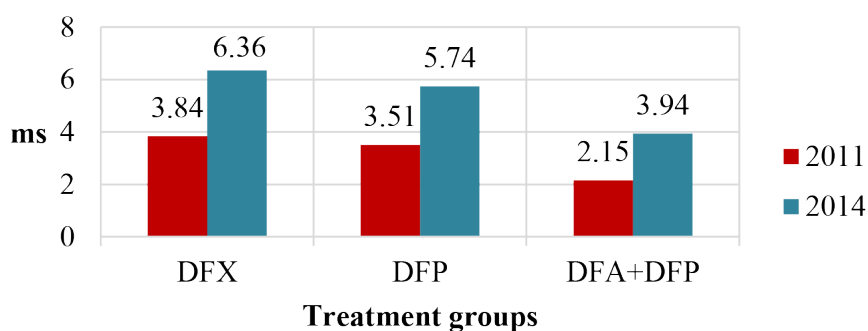


Figure 3. MRI T2* Dynamics according to the treatment modality.

Table 1. Dynamics of serum ferritin reduction according to the treatment modality

Treatment Modality	Ferritin in 2011 (mean \pm SEM) $\mu\text{g/ml}$	Ferritin in 2014 (mean \pm SEM) $\mu\text{g/ml}$	<i>p</i> value
DFX	1606 \pm	1284 \pm	0.033
DFP	1374.9 \pm	744.64 \pm	0.019
DFP+DFA	1986 \pm	1642 \pm	0.035

the proportion of patients with ferritin level above 1000 µg/ml decreased to 33.3% and the proportion of patients with moderate and severe liver siderosis – to 31%. These results are relevant to the most of the published data. Many authors consider the significant liver IO level reduction as a result of the more convenient oral forms of chelators and better adherence to therapy.^{16,17} Considering the therapeutic allocation, it should be noted that the group treated with DFP benefits the most in terms of ferritin level reduction. Comparable reduction in ferritin level is reported in the cohorts treated by DFX and DFA+DFP. Simultaneously, the average increase in MRI T2* in patients on DFX and DFP are similar, while in the group on combined therapy with DFP+DFA the observed increase remains unsatisfactory. Results similar to ours have been reported by Angulo I et al. (2008).² According to Karakas Z et al. patients with follow-up MRI examinations exhibited significant improvement in liver iron concentration, measured as increase in hepatic T2* values. The decrease of liver iron concentration was prominent in the DFX group ($p < 0.01$). The authors also report that serum ferritin level was significantly correlated with liver iron concentrations ($r_s = 0.65$, $p < 0.001$), hepatic T2* value ($r_s = -0.62$, $p < 0.001$), but not with cardiac T2* value ($r_s = -0.20$, $p = 0.07$) (18). In a one-year follow-up Vitrano A et al. found that LIC significantly decreased from MRI1 to MRI2 and 7.7% of patients shifted from LIC values of high risk to an intermediate-risk category after chelator therapy. Median change in LIC and correlation with serum ferritin levels has been reported.¹⁹ Confirmation of these important findings for a 4-year period is provided by our study in a similar population of patients. Mean T2* MRI value or mean changes in T2* MRI value after usage of iron chelators is widely reported.²⁰⁻²⁴ There is evidence that prove better control and increase of myocardial T2* MRI in those with DFP, and of liver T2* in those with good adherence to DFA chelation.²⁵ Our results do not show significant advantage of one over another treatment modality, although there is a tendency for better results in the DFP group. Larger patient cohorts and longer period of observation are needed to confirm this finding. In our analysis, the most unsatisfactory results from IO control were registered in the combined therapy group. This could be explained by the fact that the patients allocated to it were a priori showing much higher level of IO. Similar are the findings of Eghbali A et al. in a one-year follow-up.²⁶ Moreover, the subcutaneous application of DFA is a factor contributing to lower compliance to therapy. Combination chelation may be effective but adverse effects and adherence challenges limit its efficacy.

CONCLUSIONS

Patients with TM on iron-chelation therapy show stable and significant improvement of IO assessed by serum ferritin level and liver MRI T2*. This can be accounted for by the introduction of modern oral chelators in clinical

practice, their convenient oral intake, resulting in better adherence. The ease of access to accurate follow-up methods allows personalized treatment and better outcome. Oral iron chelation agents are associated with a significant reduction of iron toxicity-induced morbidity and mortality, improvement in quality of life, overall and event-free survival in transfusion-dependent patients with β -thalassemia major.²⁷

Conflict of Interest

The authors declare no conflict of interest.

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Снижение накопления избытков железа в печени у пожилых пациентов с большой β-талассемией при помощи современных методов хелатирования

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Абстракт

Введение: Контроль большой β-талассемии (БТ) требует переливания крови в течение всей жизни, что приводит к накоплению избытков железа. Удаление железа улучшается за счёт использования современных хелаторов.

Цель: Оценить влияние современной хелатной терапии посредством динамики сывороточной концентрации ферритина и МРТ T2 * печени.

Пациенты и методы: Сорок пять пациентов с БТ (соотношение мужчин и женщин 1: 1, средний возраст 33,2 ± 10,9 года) были обследованы в проспективном исследовании в период с 2011 по 2014 год. Двадцать один пациент (45,7%) проходил лечение деферазироксом, 17 (37%) - деферипроном и 8 (17,3%) - деферипроном в сочетании с дефероксамином. Ферритин был измерен с помощью ELISA. МРТ T2 * выполняли с помощью Siemens Magnetom Avanto 1.5T. Пациенты были разделены на три группы в зависимости от исходного уровня ферритина и МРТ T2 * печени. Статистический анализ проводился с использованием SPSS v. 18 для Windows. Данные были проанализированы с помощью описательного анализа, анализа дисперсии и анализа соотношения, значения были сопоставлены с использованием Т-теста и one-way ANOVA.

Результаты: В 2011 году у 9 (19,5%) пациентов была нормальная МРТ T2 * печени; в 2014 году их было 17 (37%). Пациентов с лёгким сидерозом печени было 12 (26%) в 2011 году и 14 (30,4%) в 2014 году. В 2011 году количество пациентов с умеренным сидерозом печени составило 14 (30,4%), а в 2014 году - 12 (26,0%). Одиннадцать пациентов (23,9%) имели тяжёлый сидероз печени в 2011 году, и только у двух пациентов (4,0%) было диагностировано заболевание в 2014 году.

Заключение: Снижение накопления избытков железа было установлено во всех изученных группах. Положительный эффект объясняется использованием современных хелаторов и облегчённым доступом к точному мониторингу.

Ключевые слова

большая β-талассемия, накопление избытков железа в печени, ферритин, МРТ T2 *
