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Comparative study between the effect of Desferal and Exjade as a chelating drugs in patients with B-thalassemia major

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Abstract
Background: Excess iron reserves from repeated transfusions cause various difficulties in B-thalassemia major patients. Hepatic, cardiac, and endocrine dysfunction, growth, sexual maturation, and survival are improved by chelating therapy in iron excess patients. The study aims to examine the impact of these medicines on serum ferritin levels and their effectiveness in decreasing them. These medicines affect kidney, hepatic, white blood cell, and platelet functioning.
Methods: This retrospective study at the Inherited Blood Disorder Center in Babylon reviewed 62 β-thalassemia major patients aged 1-14 years, assessing chelation therapy with deferoxamine followed by deferasirox. Evaluations included serum ferritin levels, liver and kidney function tests (ALT, AST, B. urea, S. cr., PPT, WBCs) initially and at 6, 12, and 18 months post-treatment switch. The study aimed to understand the effectiveness and safety of transitioning chelation agents in managing iron overload.
Results: Patients with B-Thalassemia major had a mean age of 9.31±2.02 years, with 78.4% older than 10 years. There were 27 (52.9%) male B-Thalassemia significant patients. The male-female ratio was 1.13:1. The initial 6-month serum ferritin value after deferral and Exjade was significantly different. (p<0.001). Significant mean serum ferritin variations (p<0.001) were seen following delay and Exjade treatment at 12 and 18 months.
Conclusion: The study found a significant reduction in serum ferritin levels when using Exjade therapy compared to Desferal. However, there were no significant changes in serum creatinine, ALT, AST, platelets, and WBC levels between Exjade and Desferal therapies. This indicates Exjade 's effectiveness in reducing iron overload without adversely affecting liver function, kidney function, or blood counts.

Keywords: Comparative, effect, Desferal, Exjade, chelating, drugs, B-thalassemia major

Introduction
Thalassemia syndromes represent a group of inherited hemolytic anemias, distinguished by defects in the synthesis of one or more globin chain subunits within the hemoglobin tetramer [1]. This condition was first detailed in 1925 by Thomas Cooley and Pearl Lee, who identified a severe form of anemia, primarily seen in children of Italian descent, characterized by splenomegaly and distinct bone changes [2]. Subsequent decades saw the identification of milder forms by various Italian researchers [3], leading to the adoption of the term "thalassemia," derived from "thalassa," the Greek word for sea, reflecting its Mediterranean prevalence [4]. Over time, α and β-thalassemias, which result from impaired synthesis of α and β-globin chains, respectively, have been acknowledged as among the most common monogenic diseases worldwide [5]. The distribution of thalassemia is extensive, spanning from the Mediterranean and certain African and Middle Eastern regions to the Indian subcontinent and Southeast Asia. β-thalassemia, in particular, exhibits gene frequencies ranging from 2% to 30% in some Mediterranean locales, though it can appear sporadically across all racial groups [6]. The molecular pathology of β-thalassemia involves mutations in the β-globin gene on chromosome 11p15.5, leading to either the absence of β-globin chains (β^0-thalassemia) or reduced synthesis (β^+-thalassemia), with nearly 200 different mutations identified [7, 8]. The disease's cellular pathophysiology is characterized by an imbalance in globin chain synthesis, leading to ineffective erythropoiesis and hemolysis [9]. This imbalance causes severe anemia in β-thalassemia major, the most severe form, presenting within the first year of life with symptoms like failure to thrive, infections, and

hepatosplenomegaly [10]. A major complication of β-thalassemia is iron overload, resulting from increased gastrointestinal iron absorption and the iron content of transfusion blood, leading to organ damage [11, 12]. Management strategies for β-thalassemia major include regular blood transfusions to manage anemia and chelation therapy to prevent iron overload [10]. Deferoxamine, a key chelation therapy agent, has significantly improved survival and quality of life but has limitations due to its administration route and side effects [13]. Oral chelators like deferasirox and deferiprone offer alternatives, with deferiprone showing effectiveness in removing cardiac iron [14, 15]. Bone marrow transplantation offers a potential cure for select patients [16], with the success rate varying based on pre-transplantation organ damage and iron levels [17]. Preventative measures, including carrier screening and prenatal diagnosis, have significantly reduced the birth of affected children in areas with high disease prevalence [18]. The investigation's objectives are to determine the efficacy of these medications in reducing serum ferritin levels. As well as white blood cells and platelets, these medications affect renal and hepatic function tests.

Methods

This retrospective study, conducted at the Inherited Blood Disorder Center in Babylon Teaching Hospital of Maternity and Children, Babylon province, from December 1, 2014, to July 31, 2015, aimed to review the treatment outcomes of patients with β-Thalassemia Major. Out of 275 thalassemia patients attending the center, 62 were identified as having β-Thalassemia Major and were initially treated with Deferoxamine (Desferal) before switching to Deferasirox (Exjade) due to insufficient response or increased serum ferritin levels. These patients, ranging from 1 to 14 years old from both sexes, underwent a regular monthly blood transfusion regimen and received Deferoxamine subcutaneously at a dose of 30-50 mg/kg for 8 hours five days per week. The study followed their serum ferritin levels, ALT, AST, blood urea, serum creatinine, platelets, and WBC counts at baseline, 6, 12, and 18 months after initiating treatment. Eleven patients were excluded due to irregular follow-up (6 patients), age above 15 years (3 patients), or use of combined chelating therapy (2 patients). The transition to Deferasirox, administered orally at a dose of 20-40 mg/kg/day, was decided by the treating doctors based on the lack of response or increase in serum ferritin levels with Deferoxamine treatment. Patients not adhering strictly to either treatment protocol or switching treatments within less than 6 months were also excluded from the study, partly due to the limited availability of Desferal pumps. Data analysis was performed using SPSS version 20, employing One-Way ANOVA for comparing more than two continuous variables over time, paired sample t-tests for comparing two readings of continuous variables, and independent sample t-tests for comparing two continuous variables at different times. A p-value of ≤0.05 was considered statistically significant, aiming to determine the efficacy and safety of transitioning from Deferoxamine to Deferasirox in managing β-Thalassemia Major.

Results

The overall mean age of B-Thalassemia major patients was (9.31+2.02) years and 40 cases (78.4%) of patients were older than 10 years as shown in (Figure 1). There were 27 cases (52.9%) of B-Thalassemia major patients were males as in (Figure 2). Male: female ratio was 1.13:1.

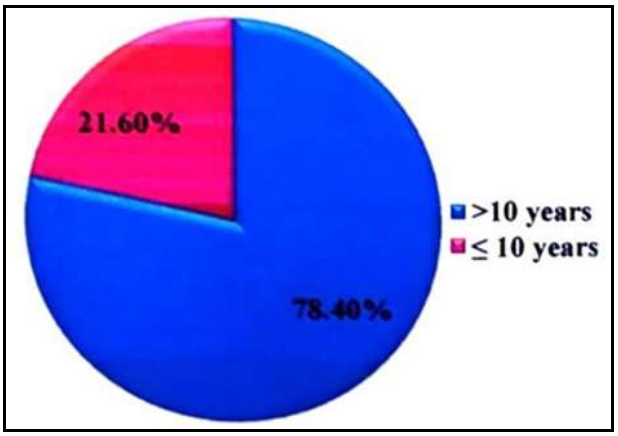

Fig 1: Distribution of B-thalassemia major patients by age groups

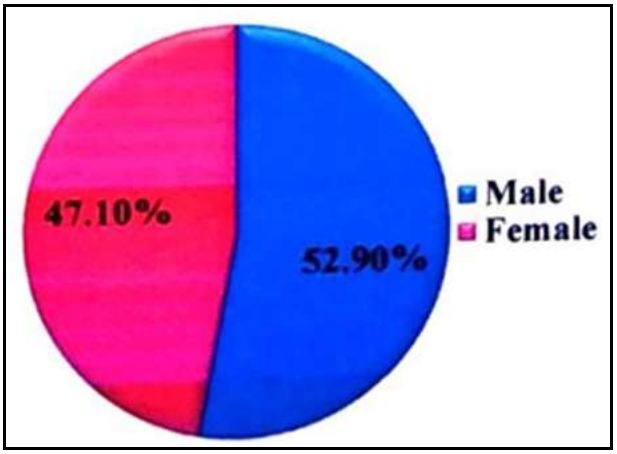

Fig 2: Distribution of B-thalassemia major patients by sex

Table 1 shows the distribution of B-Thalassemia major patients' parameters after taking Desferal according to initial, 6 months, 12 months and 18 months' interval readings.

Table 1: Distribution of β-thalassemia major patient's parameters after taking Desferal

Variable	Initial Reading (Mean ± SD)	6 Months Reading (Mean ± SD)	12 Months Reading (Mean ± SD)	18 Months Reading (Mean ± SD)
Serum ferritin (mg/L)	1989.61±870.99	2608±937.59	3383±1369.34	3790±1561.36
ALT (U/L)	13.63±13.37	13.51±7.38	13.37±7.75	17.76±22.65
AST (U/L)	11.06±4.96	11.78±6.14	11.96±5.89	13.12±11.15
Blood Urea (Mmol/L)	4.19±0.92	4.29±1.30	4.49±1.08	3.92±1.01
Serum Creatinine (Micromol/L)	54.55±10.51	55.61±8.98	53.29±11.38	56.88±12.72
Platelets (Ppt*10^9 /L)	258.04±107.61	247.64±114.71	257.41±101.02	243.02±120.49
WBC (WBC*10^9/L)	7.54±1.73	7.12±1.81	7.43±1.80	7.29±1.91

Table 2 shows the distribution of B-Thalassemia major patients' parameters after stopping Desferal and starting Exjade therapy according to initial, 6months, 12 months and 18 months' interval readings.

Table 2: distribution of β-thalassemia major patient's parameters after taking Exjade

Variable	Initial Reading (Mean ± SD)	6 Months Reading (Mean ± SD)	12 Months Reading (Mean ± SD)	18 Months Reading (Mean ± SD)
Serum ferritin (mg/L)	3790.39±1561.36	3003.59±1101.03	2276.82±904.67	1823.67±866.24
ALT (U/L)	17.76±22.65	12.98±6.44	11.80±6.64	10.98±7.12
AST (U/L)	13.12±11.15	11.93±5.18	11.19±4.64	11.70±11.01
Blood Urea (Mmol/L)	3.92±1.01	4.16±1.29	3.89±1.09	4.36±1.18
Serum Creatinine (Micromol/L)	56.88±12.72	55.33±10.58	53.43±13.95	55.23±13.33
Platelets (Ppt*10^9 /L)	243.02±120.49	250.92±76.64	259.96±83.73	289.64±129.25
WBC (WBC*10^9/L)	7.29±1.91	7.40±2.05	7.44±2.18	7.48±2.27

Table 3 shows the mean differences of B-Thalassemia major patients' parameters by Desferal and Exjade at initial reading. There was significant mean difference of serum ferritin after taking deferral and Exjade at initial reading. (p<0.001) (No significant difference in other parameters)

Table 3: Mean Differences of B-Thalassemia major Patients' Parameters between Desferal and Exjade at Initial Reading showed the initial reading of S. ferritin when starting the Desferal & Exjade therapy

Parameter of Initial reading	Chelating Agents	Mean	S.D	Paired t-test	p value
S. ferritin mg/L	Desferal	1989.60	870.99	12.209	< 0.001*
	Exjade	3790.39	1249.73		
ALT U/L	Desferal	13.62	13.37	1.189	0.240
	Exjade	17.76	22.65		
AST U/L	Desferal	11.05	4.95	1.308	0.197
	Exjade	13.11	11.15		
B. urea Mmol/L	Desferal	4.19	0.91	1.622	0.111
	Exjade	3.92	1.01		
S. creatinine Micromole/L	Desferal	54.54	10.50	1.061	0.294
	Exjade	56.88	12.72		
Ppt *10^9 /L	Desferal	258.03	107.60	1.087	0.282
	Exjade	243.01	120.48		
WBC * 10^9 /L	Desferal	7.54	1.73	0.733	0.467
	Exjade	7.29	1.91		

Table 4 shows the mean differences of B-Thalassemia major patients' parameters by Desferal and Exjade at 6 months reading. was significant mean difference of serum ferritin after taking deferral and Exjade at 6 months. (p<0.001)

Table 4: Mean Differences of B-Thalassemia Major Patients' Parameters between Desferal and Exjade at 6 months Reading showed the initial reading of S. ferritin after 6 months from starting the Desferal & Exjade therapy

Parameter of 6 months reading	Chelating Agents	Mean	S.D	Paired t-test	p value
S. ferritin mg/L	Desferal	2608.92	937.59	3.734	< 0.001*
	Exjade	3003.58	1101.03		
ALT U/L	Desferal	13.50	7.37	0.422	0.675
	Exjade	12.98	6.44		
AST U/L	Desferal	11.78	6.14	0.399	0.692
	Exjade	11.39	5.18		
B. urea Mmol/L	Desferal	4.28	1.29	0.506	0.615
	Exjade	4.16	1.28		
S. creatinine Micromole/L	Desferal	55.60	8.98	0.130	0.897
	Exjade	55.33	10.58		
Ppt *10^9 /L	Desferal	247.64	114.71	0.194	0.847
	Exjade	250.92	76.63		
WBC * 10^9 /L	Desferal	7.11	1.80	0.833	1.409
	Exjade	7.40	2.04		

Table 5 shows the mean differences of B-Thalassemia major patients' parameters by Desferal and Exjade at 12 months reading. There were significant mean differences of serum ferritin and blood urea after taking deferral and Exjade at 12 months reading. (Not significant statically).

Table 5: Mean Differences of B-Thalassemia Major Patients' Parameters between Desferal and Exjade at 12 months Reading showed the initial reading of S. ferritin after 12 months from the starting of Desferal & Exjade therapy

Parameter of 12 months reading	Chelating Agents	Mean	S.D	Paired t-test	p value
S. ferritin mg/L	Desferal	3383.39	1369.34	8.826	< 0.001
	Exjade	2276.82	904.67		
ALT U/L	Desferal	13.37	7.75	1.267	0.211
	Exjade	11.80	6.64		
AST U/L	Desferal	11.96	5.89	0.765	0.448
	Exjade	11.19	4.63		
B. urea Mmol/L	Desferal	4.49	1.08	1.146	0.334
	Exjade	3.89	1.08		
S. creatinine Micromole/L	Desferal	53.29	11.38	0.052	0.959
	Exjade	53.43	13.95		
Ppt $*10^9$ /L	Desferal	257.41	101.02	0.193	0.848
	Exjade	259.96	83.72		
WBC * 10^9 /L	Desferal	7.43	1.79	0.015	0.988
	Exjade	7.44	2.17		

Table 6 shows the mean differences of B-Thalassemia major patients' parameters by Desferal and Exjade at 18 months reading. There were significant mean differences of serum ferritin, ALT, blood urea and ppt after taking deferral and Exjade at 18 months reading.

Table 6: Mean Differences of B-Thalassemia major Patients' Parameters between Desferal and Exjade at 18 months Reading showed the initial reading of S. ferritin after 18 months from starting the Desferal & Exjade therapy

Parameter of 18 months reading	Chelating Agents	Mean	S.D	Paired t-test	p value
S. ferritin mg/L	Desferal Exjade	3790.39 1823.66	1249.73 866.23	19.830	< 0.001*
ALT U/L	Desferal Exjade	17.76 10.98	22.65 7.12	2.377	0.212
AST U/L	Desferal Exjade	13.11 11.70	11.15 11.00	0.701	0.487
B. urea Mmol/L	Desferal Exjade	3.92 4.36	1.01 1.17	2.214	0.311
S. creatinine Micromole/L	Desferal Exjade	56.88 55.23	12.72 13.32	0.622	0.537
Ppt $*10^9$ /L	Desferal Exjade	243.01 289.64	120.48 129.25	1.091	0.234
WBC * 10^9 /L	Desferal Exjade	7.29 7.47	1.91 2.26	0.605	0.458

Discussion

This study focuses on the critical issue of iron overload in patients with β-thalassemia major, a common complication arising from repeated blood transfusions. It underscores the importance of accurately assessing iron stores to tailor chelation therapy effectively. While serial serum ferritin levels serve as a convenient screening method to observe trends in iron balance, they may not precisely quantify iron stores, indicating the need for more definitive assessment tools. Chelation therapy plays a pivotal role in managing iron overload, significantly improving liver, cardiac, and endocrine function, enhancing growth and sexual maturation, and extending the life expectancy of patients with β-thalassemia major. This study evaluated the efficacy of two chelating agents, Deferoxamine (Desferal) and Deferasirox (Exjade), in a cohort of patients with an average age of 9.31±2.02 years, showing a male-to-female ratio of 1.13:1. This demographic is comparable to a study in Lahore by Tazeen Mageed [19], which reported a ratio of 1.09:1. Over an 18-month period, patients initially treated with Deferoxamine at doses of 30-50 mg/kg showed an increase in serum ferritin levels. However, upon switching to Deferasirox at a daily oral dose of 20-40 mg/kg, a significant decline in serum ferritin levels was observed, from 3790.79 mg/l to 1823.66 mg/l (p<0.001), corroborating findings from several studies [20-22]. This suggests that Deferasirox, due to its oral administration and once-daily dosing, might offer better patient compliance and effectiveness in reducing iron overload compared to the more cumbersome subcutaneous administration of Deferoxamine. The study also explored the effects of both chelators on liver function, as measured by AST and ALT levels, and found no significant differences between treatments [23]. This contrasts with findings from Ashraf Soliman *et al.* [24], who observed a significant decrease in ALT & AST levels associated with iron ferritin reduction in patients treated with Deferasirox. The discrepancy could be attributed to the small sample size or the study's short duration. Regarding kidney function, assessed through blood urea and serum creatinine levels, no significant changes were observed in patients treated with either Deferoxamine or Deferasirox, aligning with findings from Amira A-M Adly *et al.* [25]. However, other research indicates potential increases in these markers during chelation therapy [26-28], suggesting variability that could be due to the number of participants or follow-up length. Finally, the study found that WBC and platelet counts remained stable in patients on either chelation therapy over the 18-month period, a finding supported by Jalaluddin A. Khan [29] and Mohammed A. Molavi *et al.* [30]. This stability

further underscores the safety profile of both Deferoxamine and Deferasirox in managing hematological parameters in β-thalassemia major patients. This study highlights the efficacy of Deferasirox in reducing iron overload in β-thalassemia major patients compared to Deferoxamine, with no significant adverse effects on liver and kidney function or hematological parameters. The ease of use and patient compliance with Deferasirox offers a compelling argument for its preference in managing iron overload, though further research with larger patient cohorts and longer follow-up periods may provide deeper insights into the long-term outcomes of chelation therapy.

Conclusion

The use of Exjade therapy results in a notable decrease in serum ferritin levels compared to Desferal. Additionally, no significant differences were observed in serum creatinine, ALT, AST, platelets, and WBC counts between patients treated with Exjade and those treated with Desferal.

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