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Original Article

Jadenu® Substituting Exjade® in Iron Overloaded β-Thalassemia Major (BTM) Patients: A Preliminary Report of the Effects on the Tolerability, Serum Ferritin Level, Liver Iron Concentration and Biochemical Profiles

Mohamed A Yassin[1], Ashraf T Soliman[2], Vincenzo De Sanctis[3], Radwa M Hussein[4], Randa Al-Okka[4], Nancy Kassem[4], Rula Ghasoub[4], Ahmed Basha[4], Abdulqadir J Nashwan[5] and Ahmad M. Adel[4].

[1] Hematology Section, National Center for Cancer Care and Research, Hamad Medical Corporation, (HMC), Doha, Qatar.
[2] Departments of Pediatrics, University of Alexandria, Alexandria, Egypt.
[3] Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy.
[4] Pharmacists, Department of Pharmacy, National Center for Cancer Care and Research, Hamad Medical Corporation (HMC), Doha, Qatar.
[5] Nurse Research Scientist, Cancer Clinical Trials Unit, National Center for Cancer Care and Research, Hamad Medical Corporation (HMC), Doha, Qatar.

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Abstract. ***Introduction:*** **Due to the chronic nature of chelation therapy and the adverse consequences of iron overload, patient adherence to therapy is an important issue. Jadenu ® is a new oral formulation of deferasirox (Exjade ®) tablets for oral suspension. While Exjade® is a dispersible tablet that must be mixed in liquid and taken on an empty stomach, Jadenu ® can be taken in a single step, with or without a light meal, simplifying administration for the treatment of patients with chronic iron overload. This may significantly improve the compliance to treatment of patients with β-thalassemia major (BMT). The aim of this study was to evaluate the drug tolerability and the effects of chelation therapy on serum ferritin concentration, liver iron concentration (LIC) and biochemical profiles in patients with BMT and iron overload.**

Patients and Methods: **Twelve selected adult patients BMT (mean age: 29 years; range:15-34 years) were enrolled in the study. All patients were on monthly regular red cell transfusion therapy to keep their pre-transfusional hemoglobin (Hb) level not less than 9 g/dL. They were on Exjade® therapy (30 mg/kg per day) for two years or more before starting Jadenu® therapy (14-28 mg/kg/day). The reason for shifting from Deferasirox® to Jadenu® therapy was lack of tolerability, as described by patients, such as nausea, vomiting, diarrhea, stomach pain. Most of them also reported that Deferasirox® was not palatable. Lab investigations included monthly urine analysis and measurement of their serum concentrations of creatinine, fasting blood glucose (FBG), serum ferritin, alkaline phosphatase (ALP), alanine transferase (ALT), aspartate transferase (AST) and albumin concentrations. LIC was measured using FerriScan ®. Thyroid function, vitamin D and serum parathormone, before and one year after starting Jadenu ® therapy, were also assessed.**

Results: **Apart from some minor gastrointestinal complaints reported in 3 BMT patients that did not require discontinuation of therapy, other side effects were not registered during the treatment. Subjectively, patients reported an improvement in the palatability of Jadenu® compared to Exjade® therapy in 8 out of 12 BMT patients. A non-significant decrease in LIC measured by FerriScan® and serum ferritin levels was observed after one year of treatment with Jadenu®. A significant positive correlation was found between serum ferritin level and LIC measured by the FerriScan® method. LIC and serum ferritin level correlated significantly with ALT level ($r = 0.31$ and 0.45 respectively, $p < 0.05$). No significant correlation was detected between LIC and other biochemical or hormonal parameters.**

Conclusions: **Our study shows that short-term treatment with Jadenu ® is safe but is associated with a non-significant decrease in LIC and serum ferritin levels. Therefore, there is an urgent need for adequately-powered and high-quality trials to assess the clinical efficacy and the long-term outcomes of new deferasirox formulation.**

Keywords: Thalassemia major, Chelation therapy, Deferasirox, Liver iron concentration, Serum ferritin, Patient's satisfaction, Adverse events.

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Correspondence to: Mohamed A Yassin, MD. Consultant Hematologist, Hematology Section, National Center for Cancer Care and Research, Hamad Medical Corporation, Doha (Qatar). E-mail: Yassinmoha@gmail.com

Introduction. In patients with β-thalassemia major (BTM), iron overload is the joint outcome of multiple blood transfusions and an inappropriately increased iron absorption. In BTM patients, the rate of transfusional and gastro-intestinal (GI) tract iron accumulation is generally 0.3-0.6 mg/kg per day.[1] Increased GI tract iron absorption can result from severe anemia and ineffective erythropoiesis (IE), which down-regulate the synthesis of hepcidin, a protein that controls iron absorption from the GI tract and the release of recycled iron from macrophages.[2] Without correction, iron overload can lead to end-organ damage, resulting in cardiac, hepatic, and endocrine dysfunction/ failure.

Iron chelation has been proven to decrease organ dysfunction and to improve survival in certain transfusion-dependent anemias, such as β-thalassemia.[3] To date, there are 3 major classes of iron chelators: hexadentate (deferoxamine [DFO], Desferal®, Novartis Pharma AG, Basel, Switzerland), in which 1 atom of iron is bound to 1 DFO molecule; bidentate (deferiprone, [DFP] Ferriprox®, Apotex Inc., Toronto, ON, Canada), in which 1 atom of iron is bound to 3 DFP molecules; and tridentate (deferasirox [DFX], Exjade® and Jadenu®, Novartis Pharma AG, Basel, Switzerland) , in which 1 atom of iron is bound to 2 DFX molecules.[4] The intensive demands and uncomfortable side effects of therapy can have a negative impact on daily activities and well-being, which may affect adherence to treatment.[5]

Exjade® is a once-daily, oral iron chelator that was developed out of a need for a long-acting, conveniently-administered chelator for patients with transfusional hemosiderosis. The approved mode of administration requires taking Exjade® on an empty stomach with water, apple juice or orange juice to limit variation in bioavailability. Any residual medication must be resuspended in a small volume of liquid and taken. This procedure leads to a lengthy mixing process and the theoretical risk of patients not completely taking the intended dose. Additionally, one third of patients find Exjade® as a tablet for oral suspension unpalatable.[6] Additionally, approximately one-quarter of patients experience mild to moderate GI symptoms, which may pose additional challenges, particularly in the younger and older age ranges.[7]

The new tablet DFX formulation (Jadenu®) was developed in an attempt to overcome these tolerability issues and is the only once-daily oral iron chelator that can be swallowed with a light meal, without the need to disperse into a suspension prior to consumption. It was approved by the FDA on March 31, 2015.[8] The recommended initial dose of Jadenu® for patients 2 years of age and older, with estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m^2, is 14 mg/kg/body weight given orally, once daily, and titrated up by 3.5–7 mg/kg/day. In patients not adequately controlled with doses of 21 mg per kg/day (e.g., serum ferritin levels persistently above 2,500 µg/L and not showing a decreasing trend over time), doses of up to 28 mg per kg may be considered. Doses above 28 mg per kg are not recommended.[9,10]

When converting a patient from Exjade® to Jadenu®, the dosage should be decreased by 30% since the new formulation is more bioavailable than the original Exjade® formulation.[9,10]

Up to now, the new DFX formulation has been evaluated in pharmacokinetic studies in healthy volunteers in an open-label, phase II ECLIPSE study, over 24 weeks in chelation-naïve or pre-treated patients (aged >10 years) with transfusion-dependent thalassemia or myelodysplastic syndromes.[11] Patients reported greater adherence and satisfaction, better palatability and fewer concerns with Deferasirox® than Jadenu®. Treatment compliance by pill count was higher with latter compound: 92.9% vs.85.3%.[11]

Our study aimed to evaluate the patient' satisfaction, the adverse events (AEs) and the effects of Jadenu® treatment on serum ferritin concentration, liver iron concentrations (LIC) measured by FerriScan® and biochemical profiles in BTM patients with iron overload.

Patients and Methods. A pre-selected group of twelve adult patients with BTM that couldn't tolerate Exjade® therapy were enrolled in our study. The reason for shifting from Deferasirox® to Jadenu ® therapy was the lack of tolerability as described by patients, such as nausea, vomiting, diarrhea, stomach pain. Most of them also reported that Deferasirox® was not palatable.

The mean age of patients was 29 years (range:15-34 years). Six patients were males, and 2 out of 12 patients were splenectomized. All patients were on regular packed red cell transfusion therapy to keep their pre-transfusional Hb level not less than 9 g/dL. They were on Exjade ® therapy (30 mg/kg per day) for two years or more before substitution to Jadenu® therapy. All patient started with a dose of 14 mg/kg/day then escalated to a maximum dose of 28 mg/kg/day.

The efficacy and tolerability of iron chelation therapy were regularly analyzed and recorded before the blood transfusions. Doctors, taking care of BTM patients asked, during the study, the patient's satisfaction, palatability of medicine, and the presence of side effects. Safety was evaluated by monitoring and assessing AEs, changes in laboratory parameters, and clinical observations from the start of study treatment to 30 days after the last intake of study drug.

Lab investigations included monthly urine analysis and measurement of their serum concentrations of creatinine, fasting blood glucose (FBG), serum ferritin, alkaline phosphatase (ALP), alanine transferase (ALT), aspartate transferase (AST) and albumin concentrations. LIC was measured using Ferriscan®.[12] LIC values were expressed as mg/g /dry weight and classified into: normal (LIC <3 mg/g /dry weight); mild (LIC > 3 and < 7 mg/g /dry weight), moderate (LIC > 7 and < 14 mg/g /dry weight) and severe overload (LIC ≥ 15 mg Fe/g dry weight).[12,13] In addition, thyroid function [free T4 (FT4), thyrotropin (TSH)], 25 OH vitamin D and serum parathormone (PTH) levels were measured before and one year after starting Jadenu ® therapy. All patients were on vitamin D (800 U/day) and folic acid (5 mg/day).

The paired t-Student test was used to compare lab results before versus after Jadenu® treatment. Linear regression was used to investigate a possible relation between variables (LIC vs. serum ferritin level, LIC vs. other biochemical or hormonal parameters). A p value < 0.05 was considered as significant.

Ethical approval for the study was obtained by the Ethical Committee of Hamad General Hospital. All procedures were carried out with the adequate understanding and consent of patients.

Results. Subjectively, 8 out of 12 BMT patients reported an improvement in the palatability of Jadenu® compared to Exjade® therapy. Apart from some minor gastrointestinal complaints, reported in 3 BMT patients, that did not require discontinuation of therapy, other side effects were not registered during the treatment.

A non-significant statistical decrease in serum ferritin concentration and LIC values was observed after one year of Jadenu® treatment. No significant variations were observed for urine analysis, serum creatinine, albumin, ALP, ALT, AST, FBG, thyroid function, vitamin D and PTH levels (**Tables 1** and **2**).

A significant positive correlation was found between serum ferritin level and LIC, measured by the FerriScan ® method (r= 0.61, p: 0.03). LIC and serum ferritin level were also correlated significantly to ALT level (r = 0.31 and 0.45 respectively, p < 0.05). No significant correlation was detected between LIC and other biochemical or hormonal parameters.

Discussion. There are currently four different types of iron chelator readily available for patients with thalassemia: deferoxamine/DFO (branded as Desferal), deferiprone/DFP (branded as Ferriprox®), deferasirox/DFX (branded as Exjade® and Jadenu®). Each of the four chelators offers

Table 1. Biochemical data before versus after Jadenu® treatment in patients with β-thalasemia major.

		Serum creatinine	Albumin	ALP	ALT	AST	FBG
On Exjade ®	Mean	71.25	45.75	136.00	41.08	35.75	5.75
n = 12	SD	4.88	4.69	106.04	33.65	22.84	1.10
On Jadenu ®	Mean	72.67	45.00	113.50	25.50	33.08	5.73
n = 12	SD	3.75	2.74	52.44	8.87	16.86	1.15
	P value	0.12	0.28	0.16	0.08	0.36	0.48

Legend: ALP = alkaline phosphatase (U/L); **ALT** = alanine transferase (U/L); **AST** = aspartate transferase (U/L); **FBG** = fasting blood glucose (mmol/L). The reference ranges for albumin and serum creatinine are as follows: 35-55 g/L; adult women: 0.6-1.1 mg/dL (53-97 μmol/L) - adult men: 0.7-1.3 mg/dL (80-115 μmol/L).

Table 2. Liver iron content, serum ferritin and hormonal parameters in patients with β-thalassemia major before and after Jadenu ® treatment.

		LIC	SF	TSH	FT4	PTH	Vit.D
On Exjade ®	Mean	29.47	2716.92	2.51	12.34	25.75	14.22
n = 12	SD	16.01	2101.93	1.36	1.21	3.49	3.12
On Jadenu ®	Mean	26.66	2552.80	2.44	12.41	26.20	19.78
n = 12	SD	13.48	1512.92	0.87	1.00	4.21	9.06
	P value	0.31	0.36	0.41	0.40	0.13	0.09

Legend: LIC (mg/g /dry weight) = Liver iron concentration =; **SF** (ng/ml) = Serum ferritin; **TSH** (mIU/L) = thyrotropin; **FT4** (pmol/L) = free T4 ; **PTH** (ng/mL) = serum parathormone; **Vit. D** (ng/mL) =25 OH vitamin D.

different benefits and challenges to the patients.

Usage of DFP or DFX, as oral chelator is more preferably due to its ease of use, with several studies presenting higher compliance rate in LeoGib1707patients with oral chelator compared to DFO injection (s.c. or i.v.) chelator. People treated with all chelators must be kept under close medical supervision and treatment with DFO or DFX requires regular monitoring of neutrophil counts or renal function, respectively.[14]

Patients taking DFX tablets for oral suspension (Exjade®) reported superior satisfaction scores compared to those reported by patients taking DFO, with satisfaction rates for DFX as high as 90%.[15,16] However, palatability studies showed that more than third of patients disliked DFX (Exjade®) tablets for oral suspension, with self-reported adherence to the medication varying from 67% to 85%.[17,18]

The most common side effect with DFX tablets for oral suspension is GI discomfort, with 10%–33% of patients experiencing abdominal pain, diarrhea, nausea, and/or vomiting.

However, most patients are able to tolerate these side effects, although 7% of patients cited GI side effects as a reason for stopping treatment.[17-19] As DFX can cause renal toxicity and proteinuria, creatinine should be monitored twice prior to the initiation of therapy and monthly thereafter.[9,10]

The new DFX formulation (Jadenu®) thanks to the simplification of its administration is hoped to improve patient satisfaction, and thereby adherence to treatment.[8]

Subjectively, 8 out of 12 BMT patients (66.6%) enrolled in our study reported an improvement in the palatability of Jadenu® compared to Exjade® therapy. Three out of 12 BTM patients (25%) reported nausea and abdominal discomfort on Jadenu® therapy, but none of these symptoms required discontinuation of treatment. During the study period, we did not register significant changes in serum creatinine concentrations, albumin levels, and urine analysis, as well as for glucose levels and thyroid function.

Liver iron overload and hepatic dysfunction are major side effects of chronic transfusion therapy. Measurement of LIC is the most reliable indicator of body iron load. Normal LIC values are up to 1.8 mg/g dry weight, with levels of up to 7 mg/g dry weight seen in some non-thalassemic populations without apparent adverse effects. Sustained high LIC (above 15-20 mg/g dry weight) have been linked to worsening prognosis and liver fibrosis progression.[19,20] Adequate control of LIC is linked to the risk of hepatic damage as well as the risk of extrahepatic damage.

After one year of treatment with Jadenu®, a non-significant decrease in LIC and serum ferritin

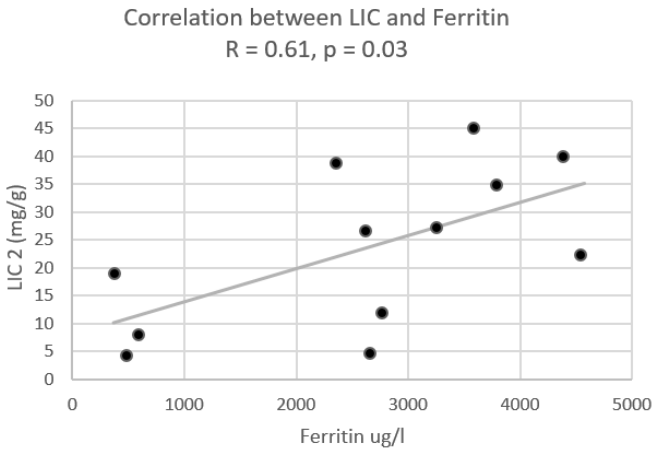

Figure 1. Linear correlation between liver iron content and serum ferritin level in patients with β-thalassemia major.

levels was observed in our patients. The term non-responder has been used to describe individuals who fail to show a downward trend in iron balance (changes in LIC) and extrahepatic iron distribution (myocardial T2*). Lack of a response of an individual may result from inadequate dosing, high transfusion requirement, poor treatment adherence, or unfavorable pharmacology of the chelation regime.[21,22]

In our patients, the dosage of oral iron chelation therapy was appropriate, the blood consumption was not increased, but the compliance to treatment was not fully evaluated, and the pharmacokinetic and pharmacodynamic profile of the new deferasirox formulation were not performed. In general, the new formulation has comparable pharmacokinetic to the dispersible tablet formulation. However, the new formulation is more bioavailable than the original Exjade®, and the peak serum concentrations (Cmax) is approximately 30% higher.[9,10]

A significant correlation between LIC assessed by FerriScan® and serum ferritin levels was observed in the current study. Although the small numbers preclude a generalization, this is in line with the findings of Zamani et al. [23] and Majd et al.[24] who reported that serum ferritin is a good parameter to detect hepatic iron loading. Serum ferritin remains an inexpensive and easily available tool for assessment of iron overload and can be used in areas where access to liver T2 MRI assessment is unavailable or limited. However, ferritin trends need to be interpreted with caution before critical changes are made in the chelation plan because trends in ferritin can be dramatically different from changes in LIC as assessed by MRI.[25]

Conclusions. Once the need for iron chelators is established in patients with transfusional iron overload, the ideal agent should be determined by the practitioner and patient. DFX (Exjade®) is a frequent choice due to ease of once-daily oral administration, but adherence may be hampered by palatability of the tablet for oral suspension.

Although some limitations are present in our study: (a) it was performed only in a single centre, and (b) the number of patients enrolled in the study was small, our results confirm that short-term treatment with Jadenu® is safe, has a better palatability and fewer patients' concerns versus the original formulation. However, it was associated with a non-significant decrease in LIC and serum ferritin levels. Therefore, there is an urgent need for further research assessing the clinical efficacy and the long-term outcomes of the new DFX formulation.

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