Renal Function in Patients with Thalassemia Major Receiving Exjade® Dispersible Tablets and a New Film-Coated Tablet Formulation of Deferasirox (Nanojade®)

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Background: In patients with β-thalassemia major (TM), one of the long-term complications of regular blood transfusion is renal dysfunction. The purpose of the current study was to evaluate the renal function in TM patients receiving Exjade® dispersible tablets and a new film-coated tablet formulation of deferasirox (Nanojade®).

Materials and Methods: In this descriptive cross-sectional study, a total of 80 TM patients aged 11–48-year-old entered the study. Patients received 20–30 mg/kg/d (single dose) Exjade® (Exjade group, n = 40) and Nanojade® (Nanojade group, n = 40) orally. To evaluated renal function, serum creatinine (S_{Cr}), estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), 24-h urine protein (U_{prot}), U_{Ca}/U_{Cr}, spot U_{prot}/U_{Cr}, ratio, and serum ferritin were calculated at baseline and every 3 months to 9 months.

Results: There was no significant difference in S_{Cr}, BUN, eGFR, 24-h U_{prot}, U_{prot}/U_{Cr}, ratio, U_{Ca}/U_{Cr}, ratio, and serum ferritin between groups at baseline and end of study (P_{baseline} > 0.05, P_{end of study} > 0.05). There was no significant difference in proteinuria between groups at baseline and end of study (P_{baseline} > 0.05, P_{end of study} > 0.05).

Conclusions: The proportion of S_{Cr}, BUN, eGFR, 24-h U_{prot}, U_{prot}/U_{Cr}, ratio, U_{Ca}/U_{Cr}, ratio was not significantly different in TM patients treated with Nanojade® compared to patients' received Exjade®. Nanojade® had similar effects to Exjade®, and therefore, the use of Nanojade® is safe in TM patients and does not seem to be associated with increased renal failure, proteinuria, and hypercalciuria.

Keywords: Deferasirox, renal function, thalassemia major

INTRODUCTION

Thalassemia is a common genetic disorder with autosomal recessive inheritance. It is carried by mutations in genes that produce the alpha or beta globin chain, eventually leading to ineffective erythropoiesis and severe microcytic hypochromic anemia. Thalassemia is highly prevalent in the Mediterranean area, Africa, Southeast Asia, and Middle East. Patients with thalassemia major (TM) become dependent on chronic blood transfusion to survive. Each 1 ml of packed red blood cells increases 1 mg of iron in TM patients receiving blood. Therefore, one of the long-term complications of regular blood transfusion is iron overload, which increases the risk of heart disease, liver disease, and endocrine dysfunction.
Following the discovery of iron-chelating drugs (ICDs), patients’ life expectancy has increased over the past few decades. ICDs are used to remove excess iron from the body and reduce the accumulation of iron in the tissues. There are currently three ICDs for clinical use: deferoxamine (DFO), which had limited oral absorption and should be administered by the subcutaneous, intravenous, or intramuscular route; deferiprone (DFP); and deferasirox (DFX).

DFX is available in several forms, including Exjade® dispersible tablets (DFX-DT, oral administration once-daily, completely dissolved in liquids and consumed 30 min before meals on an empty stomach), Jadenu® granule formulation of DFX (DFX-GF),[9] and Nanojade® a new film-coated tablets formulation of DFX (DFX-FCT) in Iran pharmaceutical market. Nanojade® is a generic drug from Jadenu® (Novartis). Unlike Exjade®, Nanojade®, and Jadenu® do not need to be dissolved in liquids and can be consumed in one step with or without a light meal.[10] The efficacy of Exjade® has already been well established in TM patients.[10]

Furthermore, improved palatability and compliance, high bioavailability, and low gastrointestinal side effects promise a better treatment with Jadenu® for a long time.[8,11] DFX-FCT is prescribed based on body weight and has three dose strengths and is available in three dose strengths (90 mg, 180, and 360 mg).[11]

The results of studies have revealed that the use of ICDs increases the risk of renal failures such as renal stones and hypercalciuria with unknown reasons.[12,13] The purpose of the current study was to evaluate the renal function in TM patients receiving Exjade® dispersible tablets and a new film-coated tablets formulation of DFX (Nanojade®) in Iran pharmaceutical market.

**Materials and Methods**

**Design and participants**

In a descriptive cross-sectional study from February 2020 to December 2020, a total of 158 patients with β- TM were enrolled at the Amir-Kabir Hospital, Arak, Iran.

Thalassemia was diagnosed based on standard methods. All TM patients received ICDs at the same time as received packed red blood cells (every 3–4 weeks). TM patients received 20–30 mg/kg/day Exjade® (Novartis) (Exjade group, n = 40) and 20–30 mg/kg/day Nanojade® (Nano Hayat Daro Pharmaceutical Company, Tehran, Iran; GTIN: 06260154636041; IRC: 2366570648796929) (Nanojade group, n = 40) orally. All ethical principles were observed according to the ethical protocol approved by the Research Ethics Committee of Arak University of Medical Sciences (IR. ARAKMU. REC.1399.200). After obtaining informed consent, TM patients aged 11–48 years were selected and included in the study. A questionnaire was designed to record patient data. All the patients were receiving Exjade® and Nanojade® before initiating the study. Patients were evaluated for 9 months. The study was done according to the Declaration of Helsinki.[14]

All ethical principles were observed according to the ethical protocol approved by the Research Ethics Committee of Arak University of Medical Sciences (IR. ARAKMU. REC.1399.200). After obtaining informed consent, TM patients aged 11–48 years were selected and included in the study. A questionnaire was designed to record patient data. Patients were evaluated for 9 months. The study was done according to the Declaration of Helsinki.

**Inclusion and exclusion criteria**

Inclusion criteria included the following: TM patients with consumption of Exjade® and Nanojade®, transfusion begins after 2 years of age, and start iron chelator treatment before 5 years of age. Study exclusion criteria included patients with hypertension, renal failure, fever, severe infection, uncontrolled diabetes, conscious dissatisfaction, liver disease, inflammatory diseases, proteinuria, oral intolerance to the drug, hepatitis B, hepatitis C, unwillingness to continue to participate in the study, and patients who refused to continue the study to the end. Eight TM patients were excluded from the study due to a lack of the mentioned conditions.

**Evaluation of renal function**

Spot urine and 24-h urine were collected from patients. Serum creatinine (U_cr), urine calcium concentration (U_ca), urine protein (U_pro), and blood urea nitrogen (BUN) were measured and recorded every 3 months up to 9 months in both groups. U_cr and U_ca were measured by kinetic Jaffe reaction and colorimetric method with methylthymol blue. U_pro and BUN were measured by biochemical kits (Pars Azmoon kits, Tehran, Iran). Then, spot U_ca/U_cr ratio and spot U_pro/U_cr ratio were calculated by dividing the U_ca to the U_cr and the U_pro to the U_cr respectively. A normal reference interval for the U_ca/U_cr ratio is <0.14 mg/mg.[15] Hypercalciuria was considered as U_ca/U_cr >0.25 mg/mg. However, the upper limit of U_ca/U_cr is controversial for accurately determining hypercalciuria.[16,17] The 24-h U_pro values ≥150 mg/dL and U_pro/U_cr ratio >0.7 mg/mg[18] are defined as proteinuria. The glomerular filtration rate (GFR) of each patient was estimated using the Schwartz equation.[19] Five milliliter of blood samples were collected to evaluate serum creatinine (S_cr) and serum ferritin levels (Advia analyzer, Siemens, Germany).

The standard range of BUN and S_cr was classified according to age and sex.[20] Normal serum ferritin level was considered 24–300 ng/ml.[21]

**Statistical analysis**

Data were analyzed using SPSS version 22 software (SPSS Inc., Chicago, IL, USA). Numerical variables are presented by the mean and standard deviation (SD). The two groups were compared using Pearson Chi-square test (or Fisher’s exact test) for qualitative variables and the student t-test for quantitative variables. Quantitative variables at different months in each group were compared using paired t-test. P < 0.05 was considered statistically significant.
RESULTS

Based on the inclusion and exclusion criteria, finally 80 patients with β− TM were selected. From a total of 80 patients with β− TM, 38 patients (47.5%) were male and 42 patients (52.5%) were female. The mean ± SD age of the patients at diagnosis was 24.37 ± 4.65 years (range: 11–48 years) and the mean ± SD follow-up time of patients was 7.32 ± 2.13 months. In Nanojade group, 40 TM patients (50%) received Nanojade® and in Exjade group, 40 patients (50%) received drug. The mean Nanojade® dose administered over the 9 months treatment period in Nanojade group was 28.3 ± 4.3 mg/kg/day and 27.9 ± 4.4 mg/kg/day in Exjade group. Demographic data of the two groups are shown in Table 1.

The parameters studied to evaluate renal function and the levels of protein at the beginning of the study in both groups were in the normal range except ferritin level which was above 1000 ng/ml in both groups and proteinuria which was positive in eight of all patients.

The mean ± SD ferritin level of the patients in Nanojade group at baseline (at the beginning of the study) was 1793.23 ± 1045.0 ng/ml. Its levels reduced from 1764.36 ± 1251.6 ng/ml after 3 months to 1597.45 ± 1110.8 ng/ml at 6 months of therapy and to 1475.25 ± 989.1 ng/ml at the end of the study; however, the decrease in serum ferritin level was not statistically significant (P > 0.05).

In Exjade group, the mean ± SD ferritin level of patients at baseline was 1353.31 ± 1094.9 ng/ml. Its levels reduced from 1347.20 ± 1076.4 ng/ml after 3 months to 1313.54 ± 1169.1 ng/ml at 6 months of therapy and to 1259.41 ± 1157.1 ng/ml at the end of the study [Table 2]; however, the decrease in serum ferritin level was not statistically significant (P > 0.05). Hence, mean ferritin levels decreased steadily in both groups during the study period. There was no significant difference between Nanojade and Exjade groups in reducing ferritin levels (P > 0.05).

In total, the mean ± SD of BUN, S$_{Cr}$, estimated GFR (eGFR), and 24-h U$_{pro}$, was 14.3 ± 4.9 mg/dl and 14.8 ± 3.9 mg/dl, respectively (P = 0.291). In total at the end of 9 months of age, 72 patients (90%) had BUN in the normal range. Eight patients (10%) had BUN above the normal range, 3 in Nanojade group (3%), and 5 in Exjade group (7%). There was no significant difference in mean BUN level between groups at baseline and the end of study (P$_{baseline} = 0.197$, P$_{end of study} > 0.291$).

At the end of 9 months of age, the mean ± SD S$_{Cr}$ level in Nanojade group and Exjade group was 0.74 ± 0.25 mg/dl and 0.72 ± 0.24 mg/dl, respectively (P = 0.242). In total at the end of 9 months of age, 74 patients (92.5%) had S$_{Cr}$ in the normal range. Six patients (7.5%) had S$_{Cr}$ levels above the normal range, 2 in Nanojade group (5%), and 4 in Exjade group (10%). There was no significant difference in mean S$_{Cr}$ level between the 2 groups at the baseline and the end of the study (P$_{baseline} = 0.101$, P$_{end of study} > 0.242$).

At the end of 9 months of age, the mean ± SD eGFR in Nanojade group and Exjade group was 108.5 ± 2.1 mL/min/1.73 m$^2$ and 108.3 ± 1.1 mL/min/1.73 m$^2$, respectively (P = 0.445). There was no significant difference in mean eGFR level between 2 groups at the baseline and the end of the study (P$_{baseline} = 0.190$, P$_{end of study} > 0.445$).

At the end of 9 months of age, the mean ± SD 24-h U$_{pro}$ in Nanojade group and Exjade group was 155.2 ± 52.8 mg/day and 154.1 ± 49.8 mg/day, respectively (P = 0.766). In total, 75 patients (93.8%) had U$_{pro}$ in the normal range at the end of 9 months of age. Five patients had U$_{pro}$ above the normal range, 2 in Exjade group, and 3 in Nanojade group. There was no significant difference in mean U$_{pro}$ level between groups at baseline and the end of study (P$_{baseline} = 0.657$, P$_{end of study} > 0.766$). Two patients in Nanojade group and 1 patient in Exjade group had a high spot U$_{pro}$/U$_{Cr}$ ratio above 0.7 mg/mg which indicates proteinuria. There was no significant difference in mean spot U$_{pro}$/U$_{Cr}$ ratio between groups at baseline and the end of study (P$_{baseline} = 0.201$, P$_{end of study} > 0.093$).

Sixteen patients in Nanojade group and 13 patients in Exjade group had a high U$_{Ca}$/U$_{Cr}$ ratio above 0.25 ratio which indicates hypercalciuria. There was no significant difference in mean U$_{Ca}$/U$_{Cr}$ ratio between groups at baseline and the end of study (P$_{baseline} = 0.784$, P$_{end of study} > 0.698$).

DISCUSSION

The results of this study showed that mean S$_{Cr}$, BUN, eGFR, and 24-h U$_{pro}$, not significantly different in patients with TM treated with Nanojade® (a new film-coated tablets formulation of DFX) and Exjade® (dispersible tablets). Furthermore, two ICDs had similar effects on serum ferritin levels in patients. However, the patients in Exjade group had lower serum ferritin levels than the Nanojade group although statistically insignificant. In our study, it was also found that in TM patients receiving two forms of DFX chelator called Nanojade® (newer form) and Exjade® (older form) for a period of 9 months, both had serum ferritin levels above 1000 ng/ml, and

Table 1: Comparison of demographic data between two groups

| Groups            | Age (years) | P    | Gender, n (%) | P    |
|-------------------|-------------|------|---------------|------|
| Exjade group      | 23.97±8.35  | 0.65b | Male: 17 (42.50) | 0.502 |
|                   | Minimum     | 11-48| Female: 23 (57.50) |      |
| Nanojade group    | 24.37±7.84a |      | Male: 21 (52.50) |      |
|                   | Minimum     | 11-39| Female: 19 (47.5) |      |

a Mean±SD, b P values were determined by student’s t-test. P values were determined by Pearson’s Chi-square test or Fisher’s exact test.
therefore, it seems that one of the disadvantages of this type of chelators compared to DFO is its lower effects on serum ferritin levels, which had been mentioned in some recent studies.\[22,23\]

In a study about the effects of DFO, DFP, and DFX on renal function in TM patients, the authors found patients receiving DFX had significantly lower serum creatinine and higher serum ferritin levels than combined chelators (DFP and DFO combination therapy), however, there was no significant difference between the two groups in terms of proteinuria.\[24\]

In another study\[25\] about the effects of DFO and DFX on the mean serum ferritin levels in TM patients aged 7–9 years, the authors found both chelators significantly decreased serum ferritin levels after 6 months, which was not consistent with the results of our study as well as the study of Economou et al.\[24\] The difference in results may be due to differences in the age of the TM patient and the time of sampling to assess

\[Table 2: Comparison of clinical data between two groups\]

| Variables                  | Months          | Nanojade group | Exjade group | P<sup>a</sup> |
|----------------------------|-----------------|----------------|--------------|---------------|
| Serum Cr<sup>b</sup> (mg/dl) | Baseline        | 0.76 (±0.16)   | 0.74 (±0.21) | 0.101         |
|                            | 3<sup>rd</sup>  month | 0.83 (±0.17)   | 0.78 (±0.23) | 0.851         |
|                            | 6<sup>th</sup>  month | 0.80 (±0.23)   | 0.73 (±0.15) | 0.123         |
|                            | 9<sup>th</sup>  month | 0.74 (±0.25)   | 0.72 (±0.24) | 0.242         |
|                            | P<sup>d</sup>: 0.358 | P<sup>d</sup>: 0.355 | P<sup>e</sup>: 0.471 | P<sup>e</sup>: 0.482 |
| BUN<sup>c</sup> (mg/dl)    | 14.5 (±4.9)     | 14.6 (±3.8)    | 0.197        |
|                            | 14.4 (±4.1)     | 14.5 (±1.9)    | 0.674        |
|                            | 14.3 (±6.6)     | 14.6 (±4.9)    | 0.18         |
|                            | 14.3 (±4.9)     | 14.8 (±3.9)    | 0.291        |
|                            | P<sup>d</sup>: 0.587 | P<sup>d</sup>: 0.507 | P<sup>e</sup>: 0.638 | P<sup>e</sup>: 0.659 |
| Ferritin<sup>c</sup> (ng/ml) | 1793.23 (±1045.0) | 1353.31 (±1094.9) | 0.061        |
|                            | 1764.36 (±1251.6) | 1347.20 (±1076.4) | 0.108        |
|                            | 1597.45 (±1110.8) | 1313.54 (±1169.1) | 0.741        |
|                            | 1475.25 (±989.1) | 1259.41 (±1157.1) | 0.848        |
|                            | P<sup>d</sup>: 0.180 | P<sup>d</sup>: 0.874 | P<sup>e</sup>: 0.081 | P<sup>e</sup>: 0.357 |
| eGFR (mL/min/1.73 m<sup>2</sup>) | 102.0±1.9      | 102.8±3.5      | 0.19         |
|                            | 105.8±3.6      | 105.1±2.6      | 0.604        |
|                            | 106.8±3.5      | 107.8±2.5      | 0.347        |
|                            | 108.5±2.1      | 108.3±1.1      | 0.445        |
|                            | P<sup>d</sup>: 0.179 | P<sup>d</sup>: 0.154 | P<sup>e</sup>: 0.098 | P<sup>e</sup>: 0.092 |
| 24 h U<sub>Pro</sub> (mg/day) | 148.1±56.1    | 147.5±43.8    | 0.657        |
|                            | 149.5±62.3    | 148.3±54.9    | 0.708        |
|                            | 151.8±49.6    | 152.3±51.6    | 0.698        |
|                            | 155.2±52.8    | 154.1±49.8    | 0.766        |
|                            | P<sup>d</sup>: 0.298 | P<sup>d</sup>: 0.201 | P<sup>e</sup>: 0.298 | P<sup>e</sup>: 0.201 |
| U<sub>Ca</sub>/U<sub>Cr</sub> ratio | 0.49±0.44    | 0.48±0.05    | 0.784        |
|                            | 0.51±0.02    | 0.50±0.10    | 0.887        |
|                            | 0.50±0.14    | 0.51±0.27    | 0.987        |
|                            | 0.52±0.25    | 0.51±0.13    | 0.698        |
|                            | P<sup>d</sup>: 0.179 | P<sup>d</sup>: 0.179 | P<sup>e</sup>: 0.098 | P<sup>e</sup>: 0.098 |
| U<sub>Pro</sub>/U<sub>Cr</sub> ratio | 0.13±0.05    | 0.16±0.09    | 0.201        |
|                            | 0.09±0.03    | 0.10±0.07    | 0.188        |
|                            | 0.06±0.02    | 0.05±0.01    | 0.241        |
|                            | 0.10±0.02    | 0.11±0.02    | 0.093        |
|                            | P<sup>d</sup>: 0.889 | P<sup>d</sup>: 0.852 | P<sup>e</sup>: 0.897 | P<sup>e</sup>: 0.753 |

\(P\) values were determined by student’s t-test between the two groups, \(\text{Mean±SD}\), \(\text{Mean and SEM}\), \(\text{Comparison of values at baseline and 6<sup>th</sup> month in each group}\), \(\text{Comparison of values at baseline and 9<sup>th</sup> month in each group}\). Cr: Creatinine, BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, U<sub>Ca</sub>/U<sub>Cr</sub> ratio: Urine calcium concentration/urine creatinine concentration ratio, U<sub>Pro</sub>/U<sub>Cr</sub> ratio: Urine protein/urine creatinine, SD: Standard deviation, SEM: Standard error of the mean
ferritin levels, as older patients have been transfused for a longer period and also considering that patients at a younger age range receive more regular treatment through their parents.

In this study, eGFR levels in both groups increased at the end of 9 months of age, however, this difference was not significant. In parallel with our study, Economou et al. showed that both DFX and DFO chelators had no significant effects on GFR compared to the control group. Several other studies have reported normal GFR in TM patients who received ICDs in the presence of renal dysfunction including proteinuria and hypercalciuria which were consistent with our findings. In our study, a total of 69 patients (86.2%) had eGFR in the normal range at the end of 9 months of age (6 in Nanojade group [15%] and 5 in Exjade group [12.5%]). However, Koren et al. showed that administration of DFO caused a statistically significant reduction in GFR in 40% of TM patients.

Furthermore, some studies have shown normal BUN, SCr, and creatinine clearance in TM patients who received ICDs.

In parallel with the findings of this study, Karimi et al. showed that DFX (Exjade®) had no significant effects on BUN level in patients compared to the control group. Karimi et al. and Aftab et al. reported that DFX is a safe and effective drug for TM patients. We also found no unfavorable effects of Nanojade® and Exjade® on renal function in this study. However, some studies have reported concerns about DFX toxicity.

In this study, the prevalence of proteinuria, by definition of spot UP/UCr >0.7, was found to be 5% in Exjade group and 7.5% in Nanojade group, with a total prevalence of 6.2%, however, this difference was not statistically significant. The prevalence of proteinuria in our study based on the spot UP/UCr ratio was slightly higher than the 24-h UP/UCr method (3.7% vs. 6.2%), which may be due to inconvenient collection or lack of proper cooperation in 24-h UP/UCr method.

It is recommended to test spot UP/UCr ratio and even urinalysis using dipstick in addition to 24-h UP/UCr in all TM patients treated with ICDs. In the study of Mohkam et al., the prevalence of proteinuria based on the spot UP/UCr ratio in TM patients after received DFO was found to be 89.3% which were higher than the prevalence found in our study. The lower prevalence of proteinuria in our study probably attributed to the type of ICDs.

In another study, about the effects of DFX (Exjade®) in TM patients aged 26 years with and without diabetes, proteinuria found 1.4% which was lower than the prevalence found in our study.

In this study, the prevalence of hypercalciuria, by definition of UCa/UCr >0.25, was found to be 32.5% in Exjade group and 40% in Nanojade group, with a total prevalence of 36.2%, however, this difference was not statistically significant. In the study of Sabzghabaei et al., hypercalciuria, by definition of 24-h urine Ca >100 mg, was found as 60% and 40% in desferal and DFX groups, respectively, with a total prevalence of 70% which was higher than the prevalence found in our study. The lower prevalence of hypercalciuria in our study might be attributed to the difference in how hypercalciuria is calculated and defined.

In another study, about the renal dysfunction in TM patients after received DFO, hypercalciuria found as 22.3% of patients. In the study of Smolkin et al., the prevalence of hypercalciuria in TM patients after received DFO was found to be 12.5% which was lower than the prevalence found in our study. One of the reasons for the different results is the differences in the type of ICDs.

**Conclusions**

The proportion of SCr, BUN, eGFR, 24-h UP/UCr, UP/UCr ratio, and UCa/UCr ratio was not significantly different in TM patients treated with Nanojade® (a new film-coated tablets formulation of DFX) and Exjade® (dispersible tablets). Nanojade® had similar effects to Exjade®, and therefore, the use of Nanojade® is safe in TM patients and does not seem to be associated with increased renal failure and proteinuria. It is suggested that in future studies, the duration of patient monitoring should be increased and more samples should be examined.

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**Conflicts of interest**

There are no conflicts of interest.

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