Experience with Combination Therapy of Deferiprone and Desferrioxamine in β-Thalassemia Major Patients with Iron Overload at Maternity and Children Hospital, Al Madinah Al Munawarah, Saudi Arabia

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Abstract
Objective
Describe our experience with combination therapy of Deferiprone (DFP) and Desferrioxamine (DFO) in treating β-Thalassemia Major patients with severe iron overload in Al Madinah Al Munawarah, Saudi Arabia and to determine any adverse events of treatment.

Methods
Twenty eight patients with β-Thalassemia major between the ages of 8 - 27 (mean 15.5 ± 4.6 years SD) were enrolled into a prospective open label one year study from January 1st 2006 to December 31st 2006, at Al Madinah Maternity & Children’s Hospital (Al Madinah Hereditary Blood Diseases Center). Participants were followed regularly at Al Madinah Hereditary Blood Diseases Center for at least 6 years prior to their enrolment in the study. The inclusion criteria were all patients who are transfusion dependent Thalassemia Major with an age of more than 8 years and serum ferretin levels > 3000 ng/L which were progressively increasing despite receiving chelating therapy with subcutaneous Desferrioxamine for at least 5 years prior to study. The doses used for Deferiprone was 75mg/kg while the dose of Desferrioxamine was 40- 50mg/kg/day. Serum ferretin and other laboratory investigations were monitored every 3 weeks and adverse events of both drugs were assessed regularly along with patients’ compliance.

Results
There was no significant reduction of serum ferretin from baseline and by the end of the study period and no serious adverse events were observed.

Conclusion
Deferiprone is a safe drug, however it did not reduce the serum ferretin from the base line, but it maintained the iron balance despite chronic transfusion in patients with β-Thalassemia major when used in combination with Desferrioxamine.

Key words: β-Thalassemia, Deferiprone, Desferrioxamine, iron overload.

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Introduction

- Thalassemia is a hereditary blood disease characterized by the absence or reduction in the synthesis of β-globins chains of the normal hemoglobin resulting in an imbalance between - and β chain and consequent ineffective erythropoeisis and hemolysis1, 2. The historical name of Cooley Anemia is the homozygous form of this disease. β- Thalassemia is endemic in all Arab countries and particularly among the Mediterranean population.

The molecular basis of β- Thalassemia in various Arab Countries reveals the presence of 52 mutations3, which are mostly of Mediterranean and Asian origin. In Saudi Arabia 14 mutation were Identified and the commonest of which is IVS-1-110 (G—A), codon 39 (C-T) and IVS 11-1 (G—A)4-7. This study was conducted in Al Madinah and the estimated gene frequency of β-Thalassemia turned out to be 0.1 %8.

Al Madinah Hereditary Blood Diseases Center was established in 1992 at Al Madinah Maternity and Children Hospital. It serves Thalassemia patients including adults in Al Madinah Region. The center provides comprehensive management that includes regular blood transfusion at 2-4 weeks intervals with regular use of Desferrioxamine (DFO).

The total of currently followed Thalassemia patients being at the center is 80. The research team first published a report on Thalassemia from Al Madinah region in 20039.

Since 1980s Desferrioxamine was the only Iron chelator used as subcutaneous infusion. The major disadvantage to this mode of therapy is its route of administration. Desferrioxamine is given subcutaneously with a special pump for 8-12 hrs everyday for at least 5 days a week placing considerable burden on the social and psychological life of the patients and their families.

Deferiprone (DFP) was the first oral Iron chelator to be licensed for use in India in 1995 and was approved as a second line drug for patients who are unable to use DFO or on whom DFO therapy had proven ineffective. Some studies10-12 have shown the effectiveness of DFP alone as an oral chelator but a combination therapy with DFO and DEP has shown to be more effective in reducing serum ferritin13-15.

Deferiprone was introduced to the Ministry of Health in Saudi Arabia in 2005 and has been used in the Thalassemia center since then. Many centers however had concerns about its safety; hence its use was not universally taken up in Saudi Arabia.

The aim of this study was to describe the experience with DFP in combination with DFO in the treatment of iron overload in β-Thalassemia patients, and to determine its safety.

Material and Methods

This is a prospective open label 1 year study of combined therapy with Deferiprone and Desferrioxamine in β thalasemic patients with iron overload.

Twenty eight patients with β-Thalassemia major were enrolled into the study over one year from January 1st 2006 to December 31st 2006, at Al Madinah Maternity & Children's Hospital (Al Madinah Hereditary Blood Diseases Center). The age ranges were 8-27 years with mean ±SD, (15 ± 4. 60) all patients were followed regularly at the Thalassemia center for at least 6 years.

Diagnosis of β-Thalassemia major was based on the clinical history of pallor, jaundice and hepatosplenomegaly with hemoglobin electrophoresis showing high HbF values (95-98%), raised HbA2 (3.5-5%) on cellulose acetate medium at alkaline PH 8.4 (Helena laboratories, 1530 Lindbergh Drive, Beaumont Texas, USA).

All patients were on chronic blood transfusion regimen receiving 10-15 ml/kg of packed red blood cells every 2-4 weeks. They had been receiving DFO (Desferal, Novartis Inc, Basel, Switzerland) at a daily dose of 40 - 50 mg/kg / day by subcutaneous infusion pump over 8-12 h for
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5 nights per week for at least 5 years prior to the study. Additional intravenous DFO (50 mg/kg body weight) was given each time at the time of blood transfusion. Desferrioxamine were started for all patients when serum ferritin level reached 1000 ng/ml. Deferiprone was added to patients with severe iron overload with serum ferritin > 3000ng/L. All patients were screened for hepatitis C virus (HCV) antibody and hepatitis B surface antigen (Hbs Ag) with appropriate standard commercial assay. During the study period no change was allowed in the dose of DFP while the DFO dose was adjusted according to the ferritin level. Informed consent was obtained from all patients and/or their parents according to their age after getting the approval of the hospital research ethics board.

**Inclusion Criteria:**
1- Transfusion-dependent Thalassemia
2- Age > 8 year
3- Serum ferritin level > 3,000 ng/L and progressively increasing undergoing chelating therapy with subcutaneous DFO for more than 5 years

**Exclusion Criteria:**
1- Severe liver, kidney or cardiac disease.
2- Serious adverse events with DFO or DFP.
3- Neutrophil count < 2000/L during the past 2 years or Platelet count < 100,000/L.
4- History of arthropathy

The Deferiprone (Ferriprox) (1, 2 dimethyl -3-hydroxypyridin -4 one) (L1) provided by Apotex Inc, (Canada) with a dose of 75 /kg/day was administered three times per day and the dose was rounded down to the nearest tablet (500mg). DFO was administered at same dose 40mg/kg/day subcutaneously twice weekly with additional intravenous dose 50mg/kg during blood transfusion. Patients were assessed for adverse events of DFP every 3 weeks and Patients were advised to temporary discontinue DFP during any febrile illness and to report to the hospital for evaluation of agranulocytosis or neutropenia.

All patients were assessed clinically and by haematological tests (Full blood count (hemoglobin, hematocrit, WBC count, absolute neutrophil count and platelet count) was performed at each 3 weekly visit. Serum ferritin level, liver and renal functions tests were measured at the beginning of the study and then every 3 months till the completion of the study. If patients developed neutropenia (defined as neutrophil count < 1000 μl) or thrombocytopenia (platelet count < 100,000 μl) DFP was temporary interrupted. If patients developed agranulocytosis (neutrophil count < 500 μl), the patients were excluded from the study. Joints pain if severe was also another cause for temporary interruption of DFP. Student’s paired \( t \)-test and analysis of variance were used to test differences of mean values and the P-values were considered statistically significant if it was < 0.05.

**Results**

Thirty patients were enrolled in the study, from which two were excluded because of development of severe gastrointestinal adverse effect with Deferiprone. Twenty eight patients successfully completed the study after 1 year: 17 males (60.7%) and 11 females (39.3%), the majority (68%) were Saudi. Sixteen patients (57%) were positive for HCV antibody, and one (3.5%) was positive for Hbs Ag. Fifteen patients (53.5%) developed mild nausea and abdominal pain with DFP, and 10 patients (35.7%) developed only mild vomiting, while skin rashes were observed in two patients (7%). One patient (3.5%) developed arthropathy and fortunately none of the patients developed neutropenia, agranulocytosis or hepatic toxicity and the drug was not interrupted in any of them. The patients’ demographic data, selected clinical parameters and drug adverse events are outlined in Table 1. The mean pre-transfusion Hemoglobin level was 7.8± 0.95 mg/dl, mean serum ferritin level at baseline
was 4450.5 ng/L and at 12 months was 4212.9 ng/L (P = 0.984), Figure 1. The mean biochemical data are given in Table 2.

Table 1: Patients clinical data and adverse events.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>60.71</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>39.24</td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
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<tr>
<td>Saudi</td>
<td>19</td>
<td>67.86</td>
</tr>
<tr>
<td>Non Saudi</td>
<td>9</td>
<td>32.14%</td>
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<tr>
<td>Consanguinity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>71.43</td>
</tr>
<tr>
<td>Good compliance with DFO</td>
<td>18</td>
<td>64.39</td>
</tr>
<tr>
<td>Good Compliance with DFP</td>
<td>15</td>
<td>53.57</td>
</tr>
<tr>
<td>HIV Infection</td>
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<td></td>
</tr>
<tr>
<td>HBV</td>
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<td>0.00</td>
</tr>
<tr>
<td>HCV</td>
<td>16</td>
<td>57.14</td>
</tr>
<tr>
<td>DFO Adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-local pain</td>
<td>18</td>
<td>62.29</td>
</tr>
<tr>
<td>-Allergy</td>
<td>16</td>
<td>57.14</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DFP Adverse events</td>
<td>15</td>
<td>53.57</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>35.71</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>53.57</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>7.14</td>
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<tr>
<td>Skin rashes</td>
<td>1</td>
<td>3.57</td>
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<tr>
<td>Arthropathy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Hepatic toxicity</td>
<td>0</td>
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</tr>
</tbody>
</table>
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Fig 1: The mean serum ferritin at baseline and at 12 months after treatment.

Table 2: The mean biochemical data at baseline and on combination (DFO+DFP)

<table>
<thead>
<tr>
<th>Items</th>
<th>Baseline on (DFO) N=28</th>
<th>Combination (DFO &amp; DFP) N = 28</th>
<th>P. Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>5.344 mmo/L</td>
<td>5.46 mmo/L</td>
<td>0.624</td>
</tr>
<tr>
<td>Sodium (Na)</td>
<td>139.5 mmo/L</td>
<td>138.6 mmo/L</td>
<td>0.414</td>
</tr>
<tr>
<td>Potassium (K)</td>
<td>4.15 mmo/L</td>
<td>4.06 mmo/L</td>
<td>0.416</td>
</tr>
<tr>
<td>Urea</td>
<td>4.12 mmo/L</td>
<td>5.74 mmo/L</td>
<td>0.366</td>
</tr>
<tr>
<td>Creatinine</td>
<td>37.41 μmo/L</td>
<td>45.37 μmo/L</td>
<td>0.008 *</td>
</tr>
<tr>
<td>AST</td>
<td>94.21 u/L</td>
<td>93.8 u/L</td>
<td>0.970</td>
</tr>
<tr>
<td>ALT</td>
<td>86.84 u/L</td>
<td>97.50 u/L</td>
<td>0.316</td>
</tr>
<tr>
<td>ALP</td>
<td>231.54 u/L</td>
<td>191.67 u/L</td>
<td>0.0009 *</td>
</tr>
<tr>
<td>T. Billirubin</td>
<td>50.86 μmo/L</td>
<td>43.90 μmo/L</td>
<td>0.110</td>
</tr>
</tbody>
</table>
Discussion

This is the first published study highlighting the local experience with Deferiprone in the treatment of patients with β-Thalassemia major with high serum ferretin receiving standard iron chelating agent Desferrioxamine in Saudi Arabia. The efficacy of the chronic use of DFO in preventing iron-induced organ damage and reducing morbidity and mortality in transfusion-dependent patients is well documented\(^{16, 17}\). However the main limitation of its use and parenteral administration using prolonged subcutaneous infusion, which frequently results in poor compliance by patients especially adolescents. Deferiprone an oral agent has recently been approved for treatment of iron overload in transfusion dependent patients\(^{18}\). Furthermore when combined with DFO significant improvement in efficacy of iron chelation has been reported\(^{15, 19, 20}\). It is hoped that this approach will improve patient’s compliance to iron chelation.

Our study shows no significant difference on serum ferretin level at 1 year after switching transfusion dependent β-Thalassemia patients with high serum ferretin on DFO alone to combination of DFP and DFO (\(P\) value of 0.984), which is consistent with other studies\(^{21, 22}\). Therefore, combination therapy had an advantage in keeping a balanced iron load in those patients with inadequate responses to DFO monotherapy, it is as effective as using DFO 5 days per week, in many recent studies of combination therapy that have demonstrated significant decrease in serum ferretin compare to DFO monotherapy\(^{23-26}\), which was demonstrated in some of the patients in this study.

Results consistent with the findings of the Cochrane systemic review 2007 which reported no consistent effect on the reduction of iron overload between treatment with Deferiprone and DFO with exception of urinary excretion. The authors recommended using Deferiprone in treating iron overload in patients with β-Thalassemia major when Desferrioxamine is either contraindicated or inadequate\(^ {27}\).

DFP showed a significant improvement in the myocardial performance as reported in many studies\(^{21, 28, 29}\).

It has been documented during the last several years that the accurate assessment of myocardial iron should be evaluated using the T2* Magnetic Resonance (MR) technique in B-Thalassemia as myocardial iron does not correlate with serum iron.

It is recommended to use MRI for assessing myocardial iron in routine clinical management of patients with β-Thalassemia major \([30]\). Cardiac evaluation was not done in this study as T2* MRI is not available in Al Madinah, nor; was echocardiography used for the assessment of myocardial performance.

None of the patients in the study developed serious adverse events, namely agranulocytosis or neutropenia which necessitate withdrawal from the study (Table 1) as observed in recent reports\(^ {22}\). The major adverse events in the study were gastrointestinal symptoms (Nausea, vomiting and abdominal pain), which were consistent with other studies\(^ {31, 32}\).

Only one patient (3.5%) developed mild arthropathy which resolved spontaneously with time. 32% of the patients in the study were non-splenectomized and none of them developed neutropenia, which contradicts others findings of significant association of neutropenia in non splenectomized patients\(^ {31}\).

There were no significant changes in ALT from baseline and after combination therapy observed (\(P\) value 0.316), but there were significant increases in serum creatinine levels when combination therapy was used (\(P\) value 0.008) but none of the patients developed renal or heart failure and this contrasts with other reports where serum creatinine remained normal\(^ {33}\).

The study demonstrates a significant reduction of serum Alkaline Phosphatase from the baseline (Table 3; \(P\) value 0.008) with no clear explanations. Hence, further studies are required to confirm or refute this finding.
The study also agrees with the Italian Society of Hematology Practice Guidelines for management of iron overload in Thalassemia major\textsuperscript{34} where the expert panel recommend that patients, who developed severe iron overload (serum ferretin>3000 ng/ml) on DFO should receive combined Iron chelating therapy and the first choice for combined therapy is DFO with DFP or to receive intensive Desferrioxamine therapy. Deferasirox (Exjade, Novartis) is a new oral iron chelator, it is orally bio-available and its half-life is between 8 and 16 hours, allowing administration once a day. It is the first FDA oral iron chelator approved in the USA in November 2005. Phase 3 trials demonstrated similar efficacy to Desferrioxamine\textsuperscript{35}, and the data revealed that chelation efficiency of Deferasirox was twice that of DFO\textsuperscript{36}. Data on cardiac iron chelation is limited although some studies have shown it is comparable to Deferiprone\textsuperscript{37, 38}.

Finally, the study agrees with the recent recommendations\textsuperscript{39} that the safety and efficacy records of DFP, DFO and their combination in particular appears to provide a universal solution in the treatment of severe iron overload and transfusion dependent Thalassemia major, as well as in reducing mortality because of their ability to clear rapidly and effectively excess cardiac Iron. However Deferasirox is to be considered as the first line oral chelator.

**Conclusion**

Deferiprone is a safe drug, however does not reduce the serum ferretin from the baseline, but it maintains the iron balance despite chronic blood transfusion in patients with β-Thalassemia major when used in combination with Desferrioxamine.

**Acknowledgement**

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