ARTICLE

Deferasirox Versus Deferoxiamine for the Treatment of Transfusional Iron Overload in Patients with β-Thalassemia Major

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Abstract

Background: Many patients with transfusional iron overload are at risk of progressive organ dysfunction and early death. Poor compliance with iron chelators is believed to be a major contributing factor. **Objectives:** The aim of this study is to evaluate the efficacy of Deferasirox in comparison with Deferoxiamine for the treatment of transfusional iron overload in patients with β-thalassemia major. **Patients and Methods:** We evaluated the once-daily Deferasirox for 48 weeks in forty patients (older than 2 years) who had β-thalassaemia major with evidence of iron overload. Some had been previously treated with chelating agents. Most patients began treatment with Deferasirox 10 mg/kg/day and may be increased to 30 mg/kg/day. Serum ferritin level was assessed before and after beginning of Deferasirox treatment at 3 months interval for 48 weeks. **Results:** Deferasirox was associated with mild adverse events on most occasions. The mean serum ferritin level decreased significantly in all patients treated with Deferasirox compared to those on Deferoxiamine. **Conclusions**: Administration of Deferasirox as an oral drug may be preferable and more effective than the parentral iron chelating therapy with better compliance and no inconvenience of parenteral infusion regimens.

Key words: Deferasirox, Deferoxiamine, Transfusional iron overload, β-thalassemia major.

Introduction

Chronic iron overload is a serious complication of the repeated blood transfusions that are necessary for the treatment of patients with blood disorders such as thalassemia, sickle cell disease, myelodysplastic syndromes and various other rare anemias such as aplastic anemia. Without chelation therapy, humans are unable to eliminate the iron released from the breakdown of transfused red blood cells, and the excess iron is deposited as hemosiderin and ferritin in the liver, spleen, endocrine organs and myocardium

leading to organ failure, particularly of the liver, heart and various endocrine glands (1,2). Diverse manifestations of iron overload are commonly seen in regularly-transfused children and adolescents with β-thalassemia. These may include growth impairment and delayed sexual maturation due to impaired pituitary function, diabetes mellitus due to iron deposition in the pancreatic islet cells, and cardiac complications later in life (3). Morbidity and mortality in regularly-transfused thalassemia patients are due primarily to the effects of iron overload rather than to the underlying disease, with over half of all deaths being attributable to cardiac complications (4). Extensive clinical research in the management of iron overload revealed that patients with thalassemia major receiving effective chelation therapy enjoy significant improvements in survival (4). Iron chelating agents mobilize tissue iron by forming soluble, stable complexes that are readily excreted in the feces and/or urine (5). Iron overload can be effectively managed by adequate chelation therapy (6). Deferoxiamine has been in clinical use for more than 40 years and is the current standard chelating agent (3). The poor oral bioavailability and short plasma half-life of Deferoxiamine necessitates parenteral administration and prolonged infusions. The standard regimen to remove excess iron accumulated through regular transfusion is inconvenient and has a negative impact on compliance and eventually on long-term outcome, with some deaths being directly attributable to poor compliance with therapy (7). Poor compliance to Deferoxiamine therapy is particularly pronounced among adolescent patients (8). There is, therefore, a clear need for an effective, well-tolerated iron chelator with a less demanding mode of administration to ensure patient compliance to life-long chelation therapy in transfusion-dependent anemia.

Patients and Methods

Patient selection

Male or female patients who are 2 or more years old with β-thalassaemia major and transfusional iron overload were studied. They required eight or more blood transfusions/year and had a serum ferritin level of 1000 ng⁄mL or greater. They were considered in two groups. Group I were those who had no iron chelating therapy before. Group II included those patients who had been treated with prior mono or combination therapy with Deferoxiamine and⁄or Deferiprone but had experienced unacceptable toxicity to Deferoxiamine, had poor response despite proper compliance with Deferoxiamine, had documented non-compliance of taking less than 50% of prescribed Deferoxiamine doses in the previous year or if Deferoxiamine treatment was contraindicated. Patients were also required to have a serum ferritin level of greater than 1000 ng⁄mL. Patients were excluded from the study if they had a mean alanine aminotransferase ; serum creatinine above the upper limit of normal; significant proteinuria; uncontrolled hypertension; chronic hepatitis B or active hepatitis C receiving specific treatment; and a history of nephrotic syndrome or any medical condition that may have affecting absorption, distribution, metabolism or excretion of Deferasirox. Patients were also excluded if they had a history of noncompliance either with treatment or the protocol (e.g. patients who were considered potentially unreliable and⁄or not cooperative).

Chelation therapy

All patients commenced Deferasirox at a dose of 10 mg/kg/day, the lowest dose of the therapeutic range found in previous Deferasirox studies. Deferasirox was administered once daily, 30 minutes before breakfast, and doses were dispersed in a glass of non-carbonated bottled water and ingested immediately. Blood transfusions were regularly administered during the study period according to the patients' requirements as judged by the investigators, with the aim of maintaining hemoglobin levels ≥8 g⁄dL.

Monitoring

Laboratory assessments were performed at least monthly and included complete blood counts, serum gamma-glutaryl-transferase, total protein, urea and creatinine. Measured Iron parameters included total iron and serum ferritin assessed monthly during the study and the change was determined using the baseline and final ferritin levels.

Statistics

The data were calculated and statistically analyzed using SPSS statistical software. A value of $P<0.05$ was considered to be statistically significant.

Results

This study included 44 β-thalassemia major patients with iron overload; 30 males and 14 females. Their ages ranged from 2 to 15 years (6.9 ± 4.1). Most of Deferasirox adverse events were mild, including transient nausea, vomiting, diarrhoea, abdominal pain and skin rash. The gastrointestinal adverse events that patients experienced with Deferasirox were generally transient in nature and lasted nor more than a week. They are all transfusion dependant with rate of transfusion per year ranging from 6

Table 1. Baseline characteristics of study groups prior to Deferasirox therapy		
Variables	Group (I)	Group (II)
Number [n (%)]	15 (34.1%)	29 (65.9%)
Age: [range in years (mean ± SD)]	2-4 (3 ± 6547)	2-15 (8.97 ± 3.65)
Gender: Males/Females	11(25%)/4 (9%)	19 (43%)/10 (23%)
Packed RBCs transfusion per year: [range (mean ±SD)]	6 -15 (10.7 ± 3.2)	6 -25 (14.9 ± 4.3)
Splenoectomized patients	None	6 (13.6%)
Base line serum ferritin: ng /mL ±SD	1647 ± 529	2131 ± 374

Table 2. Baseline serum ferritin level (ng/mL) before and (3,6,9 and 12) months after Deferasirox therapy

Variable	**Before**	**After**			
		3 months	6 months	9 months	12 months
Group I	1647 ± 529	1603 ± 538	1487 ± 479	1360 ± 419	1176 ± 457
P value		0.01	0.001	0.001	0.001
Group II	2131 ± 374	2045 ± 365	1859 ± 339	1676 ± 337	1541 ± 329
P value		0.001	0.001	0.001	0.001

The values were represented by Mean ± standard deviation. The serum ferritin values after Deferasirox therapy were compared with that before Deferasirox therapy in the corresponding group

to 25 times per year (13.5 ± 4.4). Six patients from the 44 patients were splenectomized (13.6 %), 10 patients were hepatitis C antibodies positive (22.8%) one patient was hepatitis B positive (2.3%) and two patients were positive for both C and B viruses (4.5%).

Prior to Deferasirox therapy, the patients were divided into two groups, group I did not receive any form of iron chelation before while group II were on iron chelatores Deferoxiamine and/or Deferiprone, their demographic data are summarized in table 1. Follow up serum ferritin level was measured every three month after Deferasirox therapy in which there was a significant decrease of the mean serum ferritin levels after (3,6,9,12) months of initiation

of Deferasirox therapy and were compared to that before Deferasirox therapy in both groups (Table 2).

Discussion

Chronic iron overload due to blood transfusions leads to significant morbidity and early mortality unless adequate chelation therapy is administered. Deferoxiamine is the standard chelation therapy that has a well-established safety and efficacy profile. Patients who are treated adequately with Deferoxiamine from early on in life do not develop typical complications of iron overload, including cardiac, endocrine, and hepatic failure (9). However, because Deferoxiamine must be administered by prolonged subcutaneous or intravenous infusion, patient acceptance of, and compliance with, therapy is often poor. So, despite the availability of an effective chelating agent, the compliance issues with Deferoxiamine meant that many patients still develop clinically significant iron overload, with the related impact on morbidity and mortality.

Deferasirox represents a new class of tridentate Iron chelators with a high specificity for iron (10). Evaluating the efficacy and safety of Deferasirox, dosing was based on baseline liver iron concentration (LIC) as assessed by either liver biopsy, superconducting quantum interference device (SQUID) or magnetic resonance imaging (MRI) (1). In prior studies, evaluating the efficacy and safety of Deferasirox, dosing was based on baseline LIC as assessed by liver biopsy (1). Biopsies are uncomfortable for the patient, and can get complicated by bleeding and infection (11). The consistency of results obtained from studies measuring the accuracy of LIC by SQUID is generally poor, with the underestimation of SQUID-determined LIC compared with biopsy-determined LIC being a critical factor (12). Measurement of LIC by MRI is not used routinely as it requires special software and expertise and is often unavailable or relatively expensive in many regions worldwide. Hence, serum ferritin concentration remains a convenient, less expensive and widely used way of assessing body iron and, when followed serially, is a suitable alternative marker of trends in body iron burden as significant correlations between changes in LIC and serum ferritin have been identified in various types of anemia (13). These findings support the use of regular serum ferritin assessments for the monitoring of Deferasirox therapy (14).

In the present study, we used serial serum ferritin levels to assess body iron level in thallassemic patients. Our results concur with John et al. who proposed that the compliance with the administration of parenteral Deferoxiamine chelation therapy has proved challenging to all groups of patients with transfusional iron overload (14). Deferasirox was developed in response to the need for an oral iron-chelating agent. In particular, it was desirable to have an agent that could be administered conveniently to patients of all ages, and across a range of iron burdens. Previous clinical studies indicated the potential of Deferasirox to meet this need (15). The present study was performed to compare this agent to Deferoxiamine. Because complications of chronic iron overload have been best studied in thalassemia, this group of patients was used for the demonstration of efficacy for Deferasirox.

A significantly decreased serum ferritin levels were observed in our study after the usage of Deferasirox, this obtained results are consistent with the studies of Nisbet et al and Cappellini et al. (16,13) in their previously published short-term study examining the ability of Deferasirox to remove iron from the body. The same finding was observed by Porter et al. (18) who reported that the effective administration of iron chelation therapy has been limited by the route of its administration. Although Deferoxiamine is effective in removing iron from the body, due to very poor oral bioavailability and short half-life, it must be administered by subcutaneous or intravenous infusion but the compliance with this regimen is often poor. Also Treadwell et al (18), reported that the availability of a once-daily, oral alternative Deferasirox would potentially facilitate improved compliance, and thereby reduce morbidity and mortality from iron overload. Also our results are in agreement with Elliott *et al*. and Stumpf *et al*. (19,20) who proposed that in routine clinical practice, compliance with a once-daily, oral regimen offers a promising alternative for patients unwilling or unable to comply with parenteral Deferoxiamine therapy.

In conclusion, our data provide further evidence that patients with β-thalassaemia major with iron overload may be effectively managed using an oral Deferasirox regimen that and considered to be preferable and effective than the parenteral iron chelating therapy due to the poor patient compliance and poor practical regimen of parenteral infusions especially at our region.

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