

**2009 Annual Meeting of the
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Highlights Report

**Efficacy and Safety of Deferasirox (Exjade®) in β -
Thalassemia Patients with Myocardial Siderosis: 2-
Year Results From the EPIC Cardiac Sub-Study**

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Abstract 4062

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Efficacy and Safety of Deferasirox (Exjade[®]) in β -Thalassemia Patients with Myocardial Siderosis: 2-Year Results From the EPIC Cardiac Sub-Study (Abstract # 4062)

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Heart failure due to cardiac iron deposition accounts for approximately 70% of deaths in regularly transfused patients with β -thalassemia major.^{1,2} While monitoring of total body iron markers such as serum ferritin or liver iron concentration may not accurately reflect myocardial iron status,^{3,4} magnetic resonance imaging (MRI) using the relaxation parameter T2* can be used to directly and rapidly assess iron content in the heart, and is used at over 50 centers worldwide.⁵ Cardiac T2* values corresponding to cardiac iron overload and increased likelihood of heart failure and arrhythmia have been established with a T2* >20 being associated with normal ventricular function.^{6,7} Intensive chelation therapy has been shown to reverse cardiac dysfunction due to iron overload, highlighting the importance of constant, 24-hour chelation coverage for preventing further damage to the heart.^{3,4}

One-year core data from the cardiac sub-study of the EPIC trial demonstrated the efficacy of deferasirox, an oral iron chelator, in reducing cardiac iron in 114 patients with β -thalassemia major both with severe (T2* >5–<10 ms) and mild-to-moderate (T2* 10–<20 ms) cardiac siderosis.⁸ A total of 101 patients with myocardial siderosis then entered a 1 year extension phase. The results presented here are the first to report two-year data on cardiac iron removal for any iron chelator.

Deferasirox was initiated at a dose of 30 mg/kg/day due the severity of iron overload in this patient group, with dose adjustments to a maximum of 40 mg/kg/day permitted. In total, 86 patients (85.2%) completed 2 years of therapy with deferasirox, and the mean dose over the treatment period was 34.5 mg/kg/day. At this mean deferasirox dose over 24 months, myocardial T2* improved significantly from baseline representing an increase of 40.8% ($P<0.001$). Patients with severe

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(T2* >5 – <10) and mild-to-moderate (10 – <20 ms) cardiac siderosis at baseline experienced increases in cardiac T2* from baseline of 26.8% ($P<0.001$) and 48.1%, respectively ($P<0.001$) (Table 1)

Table 1. Geometric Mean Cardiac T2* over 24 months in all patients and in subgroups with baseline T2* >5–<10 ms (severe cardiac siderosis) and 10–<20 ms (mild-to-moderate cardiac siderosis)

	Baseline	1 year	2 years	<i>P</i> value (BL – 2 years)
Severe (T2* >5-<10) (n)	7.3 (39)	8.1 (39)	9.5 (29)	<0.001
Mild-to moderate (T2* 10-<20) (n)	14.6 (62)	17.5 (62)	20.4 (56)	<0.001
All (n)	11.2 (101)	13.0 (101)	15.7 (85)	<0.001

Left ventricular ejection fraction (LVEF) remained stable ($P=0.72$), mean right ventricular ejection fraction (RVEF) increased significantly from baseline at 24 months ($P<0.001$) and right ventricular end-systolic volume (RVESV) remained stable. Liver iron concentration by R2 MRI and serum ferritin were significantly reduced in both sub-groups at 24 months by 10.7 ± 12.8 mg Fe/g dw and 2343 ng/mL (range: -12,795 – 25,127), respectively ($P<0.001$).

The incidence of investigator-assessed drug-related AEs that occurred in $\geq 5\%$ of patients did not increase in the extension phase relative to the core phase despite the increased mean deferasirox dose. In total, four patients (4.0%) had an increase in serum creatinine $>33\%$ above baseline and the upper limit of normal (ULN) on two consecutive visits; there were no progressive increases. Four patients (4.0%) had an increase in ALT >10 x ULN on two consecutive visits; levels were already elevated at baseline in all of these patients. The most common AEs requiring dose reduction were increased serum creatinine (n=23; 22.8%), increased ALT (n=6; 5.9%) and increased AST (n=6; 5.9%).

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These results show that continued therapy with deferasirox removes iron from the heart in β -thalassemia patients with mild, moderate and severe myocardial siderosis.⁹ Cardiac T2* continued to improve over 2 years of therapy and the improvement from baseline was associated with maintenance of normal cardiac function and a concomitant decrease in hepatic and total body iron burden.

Overall, deferasirox treatment was well tolerated. The safety profile was clinically manageable with deferasirox doses 30–40 mg/kg/day and there was no evidence of progressive impairment of renal or liver function; doses of 30–40 mg/kg/day may be required for heavily iron-overloaded patients. Additional evidence of the efficacy of deferasirox for removal of cardiac iron will be generated from the ongoing, randomized controlled trial 2206 of deferasirox vs DFO to treat myocardial siderosis as assessed by cardiac T2* in patients with β -thalassemia, MDS and Diamond-Blackfan anemia.

Expert commentary: Dr John Porter, University College London, UK

Experience with the use of higher doses of deferasirox has gradually increased. Analysis of safety data in this study and in others where doses up to 40mg/kg/day were given has not shown any evidence of increased or new toxicities. Provided the usual monitoring is undertaken (renal and hepatic) doses up to 40mg/kg day in patients with high levels of body iron or increased myocardial iron seem justified. There is growing evidence from prospective studies that deferasirox is effective at removing cardiac iron. This is likely to have a major impact on how we use this drug and in which patients.

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