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Optimising iron chelation therapy with deferasirox for non-transfusion-dependent thalassaemia patients: 1-year results from the THETIS study

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ABSTRACT

Efficacy and safety of iron chelation therapy with deferasirox in iron-overloaded non-transfusion-dependent thalassaemia (NTDT) patients were established in the THALASSA study. THETIS, an open-label, single-arm, multicentre, Phase IV study, added to this evidence by investigating earlier dose escalation by baseline liver iron concentration (LIC) (week 4: escalation according to baseline LIC; week 24: adjustment according to LIC response, maximum 30 mg/kg/day). The primary efficacy endpoint was absolute change in LIC from baseline to week 52. 134 iron-overloaded non-transfusion-dependent anaemia patients were enrolled and received deferasirox starting at 10 mg/kg/day. Mean actual dose ± SD over 1 year was 14.70 ± 5.48 mg/kg/day. At week 52, mean LIC ± SD decreased significantly from 15.13 ± 10.72 mg Fe/g dw at baseline to 8.46 ± 6.25 mg Fe/g dw (absolute change from baseline, −6.68 ± 7.02 mg Fe/g dw [95% CI: −7.91, −5.45]; $P < 0.0001$). Most common drug-related adverse events were gastrointestinal: abdominal discomfort, diarrhoea and nausea (n = 6 each). There was one death (pneumonia, not considered drug related). With significant and clinically relevant reductions in iron burden alongside a safety profile similar to that in THALASSA, these data support earlier escalation with higher deferasirox doses in iron-overloaded non-transfusion-dependent anaemia patients.

1. Introduction

Non-transfusion-dependent thalassaemia (NTDT) describes a group of inherited genetic disorders that affect haemoglobin (Hb) chain synthesis, leading to ineffective erythropoiesis and anaemia [1–4]. NTDT comprises several thalassaemia syndromes that do not require regular blood transfusions for survival (transfusions may be required in some instances, such as pregnancy, infection or growth failure), most commonly including β thalassaemia intermedia, Hb H disease and Hb E/β thalassaemia [5]. Despite infrequent blood transfusions, patients with NTDT are at risk of iron overload mainly because of increased iron uptake from the gastrointestinal tract [6,7], as a result of ineffective erythropoiesis, accompanied by anaemia and hypoxia [8]. While the

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; CI, confidence interval; CrCl, creatinine clearance; dw, dry weight; Hb, haemoglobin; LIC, liver iron concentration; LOCF, last observation carried forward; MRI, magnetic resonance imaging; NTDT, non-transfusion-dependent thalassaemia; SAE, serious AE; SCr, serum creatinine; SD, standard deviation; SE, standard error; TDT, transfusion-dependent thalassaemia; ULN, upper limit of normal; UPCR, urine protein/urine creatinine ratio.

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phenotypic spectrum in NTDT varies widely, the clinical sequelae of iron overload and elevated liver iron concentration (LIC) in NTDT is similar to patients with transfusion-dependent thalassaemia (TDT), including abnormal liver function, fibrosis and cirrhosis, as well as endocrine disorders [9–12].

Clinical studies have provided evidence for the efficacy and safety of iron chelation therapy in NTDT patients with iron overload [13–19]. The THALASSA study was the first randomised, placebo-controlled study demonstrating the efficacy and safety of deferasirox (Exjade®, Novartis Pharmaceuticals) in a large cohort of NTDT patients [19–22]. In the 1-year THALASSA study, deferasirox was initiated at doses of 5 and 10 mg/kg/day and increased to 10 and 20 mg/kg/day at month 6. Deferasirox 10 mg/kg/day demonstrated significantly improved efficacy over the 5 mg/kg/day regimen in reducing LIC, and nearly half of all patients required dose escalations up to 20 mg/kg/day. These findings indicated that a higher chelation dose may be required and should be initiated earlier in the course of treatment to achieve a more rapid reduction in iron burden. Both deferasirox starting doses and placebo groups had a similar safety profile and incidence of adverse events (AEs) [19]. Based on these outcomes, the Thalassaemia International Federation guidelines recommend iron chelation therapy with deferasirox in NTDT patients ≥10 years of age when LIC reaches ≥5 mg Fe/g dw (or serum ferritin ≥800 ng/mL), starting at 10 mg/kg/day. After 6 months of treatment, the dose may be escalated to 20 mg/kg/day in patients with LIC >7 mg Fe/g dw (or serum ferritin levels 1500–2000 ng/mL if LIC measurement is unavailable) and <15% reduction in baseline values [23].

Here we report 1-year data from the THETIS study, a Phase IV, open-label, multicentre efficacy and safety study of deferasirox in iron-overloaded patients with NTDT. This study adds to existing knowledge by assessing a broader patient population through allowing inclusion of patients with non-transfusion-dependent congenital or chronic anaemias in addition to the non-transfusion-dependent thalassaemias also studied in THALASSA (β thalassaemia intermedia, Hb E/β thalassaemia or α thalassaemia intermedia [Hb H] disease), concomitant medications commonly used in the treatment of NTDT syndromes, and by investigating earlier dose escalation according to baseline LIC and every 6 months according to LIC.

2. Methods

2.1. Key inclusion/exclusion criteria

Patients ≥10 years of age with non-transfusion-dependent congenital or chronic anaemias and iron overload (LIC measured by R2 magnetic resonance imaging [MRI] ≥5 mg Fe/g dw) and serum ferritin ≥300 ng/mL at screening were recruited. Ancillary treatments for NTDT, such as hydroxyurea, were allowed. Exclusion criteria included: blood transfusions within 6 months of study enrolment or anticipated regular transfusions (unplanned transfusions were allowed), Hb S variants of thalassaemia, active hepatitis B or C, cirrhosis, history of clinically relevant ocular and/or auditory toxicity related to iron chelation therapy, or on two consecutive measurements: alanine aminotransferase (ALT) > 5× the upper limit of normal (ULN), serum creatinine (SCr) > ULN, creatinine clearance (CrCl) ≤ 40 mL/min, or urine protein/urine creatinine ratio (UPCR) > 1.0 mg/mg. Paediatric patients had to weigh at least 20 kg. Patients (or parents/guardians) provided written, informed consent prior to enrolment.

2.2. Study design

THETIS is an open-label, single-arm, multicentre, Phase IV, 5-year study with the primary endpoint after 52 weeks of treatment. The starting deferasirox dose was 10 mg/kg/day, with dose increases permitted at week 4 (maximum dose of 20 mg/kg/day) and week 24 (maximum dose of 30 mg/kg/day; Fig. 1), selected based on the results from the THALASSA study. Dose decreases according to safety assessments were performed in increments of 5 mg/kg/day to a minimum of 5 mg/kg/day. If repeated serum ferritin levels were <300 ng/mL or LIC < 3 mg Fe/g dry weight (dw) at any visit, treatment was suspended, then restarted at the previous effective dose (maximum 10 mg/kg/day) when serum ferritin increased to ≥300 ng/mL and LIC to ≥5 mg Fe/g dw. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by independent ethics committees at participating sites.

2.3. Assessments

The primary endpoint was the absolute change in LIC (mg Fe/g dw) from baseline to 52 weeks, supported by analyses of the proportion of patients with an absolute LIC reduction of at least 3 mg Fe/g dw or relative reduction of ≥30%. Secondary endpoints included mean absolute change in LIC from baseline to 24 weeks, change in serum ferritin from baseline to 52 weeks, and correlation of LIC with serum ferritin at baseline and week 52.

LIC was assessed at screening, week 24 and week 52 using validated R2 MRI (FerriScan®) [24]. Serum ferritin was measured at screening, on day 1 and every 4 weeks thereafter. LIC and serum ferritin were analysed at a central laboratory.

Safety was evaluated by regular monitoring and recording of AEs and serious AEs (SAEs), laboratory testing and clinical evaluations. Compliance was estimated based on the prescribed versus dose taken, calculated using the dose administration record.

2.4. Statistical evaluations

Assuming a standard deviation of 6 mg Fe/g dw and drop-out rate of 20%, a sample size of 117 patients was calculated to obtain 90% power to detect an absolute change in LIC of ≥2 mg Fe/g dw from baseline to week 52, using a two-sided paired t-test with 5% significance level. The primary efficacy analysis utilised the full analysis set (all patients assigned study drug). If no LIC measurement was available at week 52, the last available post-baseline LIC measurement before week 52 was used (last observation carried forward [LOCF]). The null hypothesis (change from baseline to week 52 equal to 0) was tested against the alternative hypothesis. LIC change from baseline to week 24 and serum ferritin change from baseline to week 52 were analysed as secondary objectives. Correlation analyses were performed for paired LIC and serum ferritin values.

3. Results

3.1. Patient demographics and clinical characteristics

A total of 134 patients enrolled between 6 December 2012 and 22 November 2013; 112 (83.6%) completed 1 year of treatment. Patients discontinued treatment because of withdrawal of consent (n = 10, noted as personal or logistical reasons), loss to follow-up (n = 4), pregnancy (n = 4) and other reasons (death, AE, protocol deviation and patient decision, n = 1 each). The majority of patients received prior intermittent transfusion therapy (85.8%) and had elevated baseline mean LIC ± standard deviation (SD) and median serum ferritin levels; 47.8% of patients received prior chelation therapy (Table 1).

3.2. Exposure to treatment and compliance

The mean actual deferasirox dose ± SD received during the 1-year study (considering dose adjustments) was 14.70 ± 5.48 mg/kg/day over a mean duration of 11.57 ± 2.68 months. Over 1 year, 124 (92.5%) patients received dose adjustments according to the protocol, including restarts (n = 53, 39.6%), to achieve LIC < 3 mg Fe/g dw (n = 15, 11.2%) and serum ferritin < 300 ng/mL (n = 10, 7.5%). AEs