


# BMJ Open Efficacy and safety of deferoxamine, deferasirox and deferiprone triple iron chelator combination therapy for transfusion-dependent $\beta$ -thalassaemia with very high iron overload: a protocol for randomised controlled clinical trial

Anuja Premawardhena,<sup>1,2</sup> Chamodi Perera,<sup>3</sup> Muditha Nayana Wijethilaka,<sup>1</sup> Sakuni Keshani Wanasinghe,<sup>2</sup> R H M G Rajakaruna,<sup>4</sup> R A N K K Samarasinghe,<sup>4</sup> Senani Williams,<sup>5</sup> Sachith Mettananda <sup>1,3</sup>

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For numbered affiliations see end of article.

## Correspondence to

Dr Sachith Mettananda;  
sachith.mettananda@kln.ac.lk

## ABSTRACT

**Introduction** Despite the improvement in medical management, many patients with transfusion-dependent  $\beta$ -thalassaemia die prematurely due to transfusion-related iron overload. As per the current guidelines, the optimal chelation of iron cannot be achieved in many patients, even with two iron chelators at their maximum therapeutic doses. Here, we evaluate the efficacy and safety of triple combination treatment with deferoxamine, deferasirox and deferiprone over dual combination of deferoxamine and deferasirox on iron chelation in patients with transfusion-dependent  $\beta$ -thalassaemia with very high iron overload.

**Methods and analysis** This is a single-centre, open-label, randomised, controlled clinical trial conducted at the Adult and Adolescent Thalassaemia Centre of Colombo North Teaching Hospital, Ragama, Sri Lanka. Patients with haematologically and genetically confirmed transfusion-dependent  $\beta$ -thalassaemia are enrolled and randomised into intervention or control groups. The intervention arm will receive a combination of oral deferasirox, oral deferiprone and subcutaneous deferoxamine for 6 months. The control arm will receive the combination of oral deferasirox and subcutaneous deferoxamine for 6 months. Reduction in iron overload, as measured by a reduction in the serum ferritin after completion of the treatment, will be the primary outcome measure. Reduction in liver and cardiac iron content as measured by T2\* MRI and the side effect profile of trial medications are the secondary outcome measures.

**Ethics and dissemination** Ethical approval for the study has been obtained from the Ethics Committee of the Faculty of Medicine, University of Kelaniya (Ref. P/06/02/2023). The trial results will be disseminated in scientific publications in reputed journals.

**Trial registration number** The trial is registered in the Sri Lanka Clinical Trials Registry (Ref: SLCTR/2023/010).

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This randomised controlled clinical trial evaluates the efficacy and safety of the triple combination of deferoxamine, deferasirox and deferiprone versus the dual combination of deferoxamine and deferasirox in patients with  $\beta$ -thalassaemia for the first time.
- ⇒ The inclusion of a homogenous study population of patients with haematologically and genetically confirmed  $\beta$ -thalassaemia with very high serum ferritin levels improves the reproducibility of the study.
- ⇒ The efficacy of the triple combination of deferoxamine, deferasirox and deferiprone is evaluated comprehensively on multiple outcomes, including a reduction in serum ferritin, T2\* MRI of the liver and T2\* MRI of the heart.
- ⇒ Some of the study participants may have hepatic dysfunction due to iron overload; therefore, serum ferritin may not be a very reliable marker of iron overload. However, serum ferritin is still the most widely used biomarker of iron overload, even among these patients.

## INTRODUCTION

$\beta$ -Thalassaemia major is a disorder of haemoglobin synthesis which results in severe anaemia from early infancy.<sup>1</sup> It is universally fatal without blood transfusion.<sup>2</sup> Patients with transfusion-dependent  $\beta$ -thalassaemia major require regular monthly blood transfusions throughout their lives.<sup>3</sup> Regular transfusions lead to numerous medical complications, of which the body iron overload is the most problematic.<sup>4</sup> Excess transfusional iron is deposited in many organ systems, including the liver, heart, pancreas and endocrine

organs leading to organ failures and premature death in the third and fourth decades of life.<sup>5</sup>

Three iron chelator medications are currently available to chelate excess iron. They are deferoxamine, deferasirox and deferiprone.<sup>6</sup> Of these, deferoxamine and deferasirox are shown to have similar efficacies.<sup>7</sup> Deferiprone, on the other hand, has the valuable property of selectively chelating cardiac iron.<sup>8</sup> Nevertheless, none of the iron chelators is adequately effective to chelate iron fully in most patients with  $\beta$ -thalassaemia due to poor compliance and tolerability at maximum doses.<sup>9</sup> In addition, cost of medications and limitations in availability and affordability of iron chelating medications also contribute to the high iron burden. Hence, patients with transfusion-dependent  $\beta$ -thalassaemia continue to have excess free iron, which is toxic to cells leading to medical complications of the disease.<sup>10 11</sup>

Combination therapy with two iron chelators has been adequately studied and is used in patients who have high iron load despite being on the maximum dose of a single iron chelator. The combination of deferoxamine and deferasirox is known to have synergistic effects.<sup>12</sup> Similarly, the combination of deferoxamine and deferiprone is recommended.<sup>7</sup> Although data on the combined use of two oral iron chelators, deferasirox and deferiprone, are relatively less, they have been studied in clinical trials. The combination of deferoxamine and deferasirox is commonly used in Sri Lanka, while the use of deferiprone is low. Despite using a dual combination of iron chelators in their maximum doses, many patients with transfusion-dependent  $\beta$ -thalassaemia continue to have high iron overload.<sup>13</sup> This study aims to evaluate the efficacy and safety of triple combination treatment with deferoxamine, deferasirox and deferiprone over dual combination therapy with deferoxamine and deferasirox on iron chelation in patients with transfusion-dependent  $\beta$ -thalassaemia with very high iron overload.

## METHODS AND ANALYSIS

### Study design and setting

This study is an ongoing single-centre, randomised, open-label controlled clinical trial that evaluates the efficacy and safety of triple combination treatment with deferoxamine, deferasirox and deferiprone on iron chelation in patients with transfusion-dependent  $\beta$ -thalassaemia with very high iron overload. The study is conducted at the Adult and Adolescent Thalassaemia Centre of Colombo North Teaching Hospital, Ragama, Sri Lanka, which is the second largest thalassaemia centre in Sri Lanka.

### Study hypothesis

Triple combination treatment with deferoxamine, deferasirox and deferiprone is more effective in chelating iron than dual combination treatment with deferoxamine and deferasirox in patients with transfusion-dependent  $\beta$ -thalassaemia with very high iron overload.

### Study population and eligibility criteria

Patients with haematologically and genetically confirmed transfusion-dependent  $\beta$ -thalassaemia with very high serum ferritin ( $>3500$  ng/mL) attending the Adult and Adolescent Thalassaemia Centre of the Colombo North Teaching Hospital, Ragama, Sri Lanka, will be eligible for the study.

### Inclusion criteria

- ▶ Patients with transfusion-dependent  $\beta$ -thalassaemia.
- ▶ Patients requiring at least eight blood transfusions (each with a minimum volume of 20 mL/kg) during the preceding 12 months.
- ▶ Patients aged over 12 years.
- ▶ Patients with very high iron overload with serum ferritin  $>3500$  ng/mL in the last two measurements done over the preceding 3 months.
- ▶ Patients who were switched to combination therapy with deferoxamine and deferasirox due to lack of response to monotherapy.

### Exclusion criteria

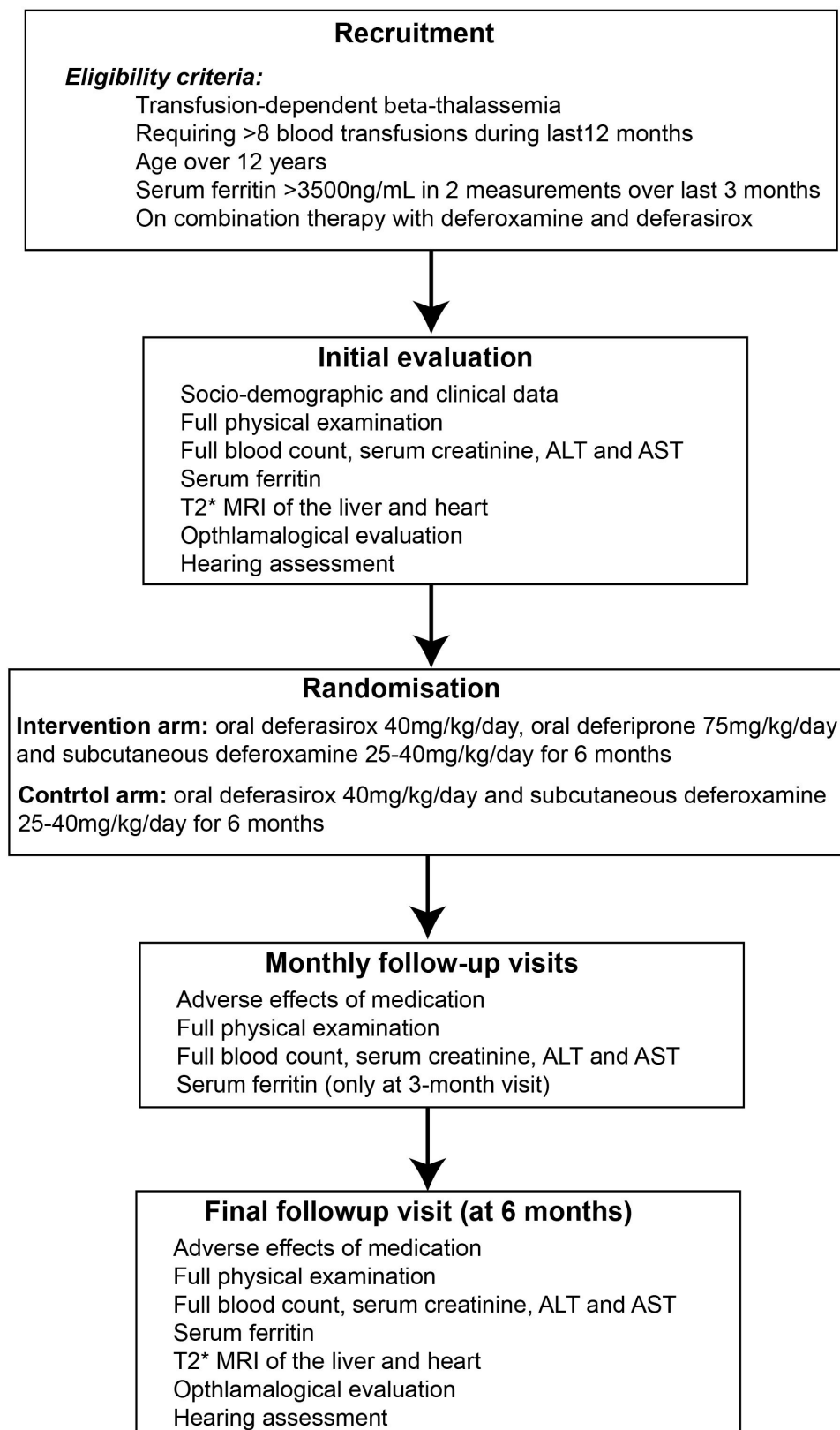
- ▶ Pregnant and lactating women.
- ▶ Children under the age of 12 years.
- ▶ History of severe adverse effects to any of the three iron chelators.
- ▶ Contraindications for any of the three iron chelators.
- ▶ Patients who have been started on regular transfusions for a predetermined limited period.
- ▶ Active hepatitis B or hepatitis C infection.

### Sample size

No previous studies report the efficacy of triple combination therapy in patients with transfusion-dependent thalassaemia. The sample size was calculated for a superiority randomised trial using an online sample size calculator (<https://riskcalc.org/samplesize/>) to detect a superiority margin ( $\delta$ ) of 0.2 and a true difference in mean serum ferritin of 500 ng/mL. To achieve an 80% power with a type I error ( $\alpha$ ) of 0.05, a type II error ( $\beta$ ) of 0.2 and a 2:1 allocation, the minimum sample size required for intervention and control arms were 12 and 6, respectively. Therefore, we aim to recruit 18 patients for this clinical trial.

### Subject enrolment, randomisation and blinding

All eligible patients who fulfil inclusion criteria will be given a patient information sheet to read and time to clarify doubts with investigators before obtaining informed written consent. When the subject is below the age of 18 years, consent will be obtained from one of the parents, and assent will be obtained from the subjects. This is an open-label trial. Patients will be randomised into two groups (intervention arm and control arm) using an online simple randomisation tool for an allocation ratio of 2:1 to intervention and control arms (figure 1).



**Figure 1** Study design and participant flow through the study. ALT, Alanine transaminase; AST, Aspartate transaminase.

### Intervention

The intervention arm will receive the combination of oral deferasirox 40 mg/kg/day, oral deferiprone 75 mg/kg/day and subcutaneous deferoxamine 25–40 mg/kg/day

at least 5–7 days per week for 6 months. The control arm will receive the combination of oral deferasirox 40 mg/kg/day and subcutaneous deferoxamine 25–40 mg/kg/day at least 5–7 days per week for 6 months.

## Study procedure

Information on sociodemographic background and clinical characteristics will be gathered at the enrolment by interviewing patients and parents and perusing patient records. Then, the patients will be reviewed at least monthly during the intervention period when they come for routine blood transfusions. Other standard treatments, including leucodepleted packed red blood cell transfusion and routine evaluation of transfusion and iron overload-related complications, will be continued as per the Thalassaemia International Federation guidelines.

During each visit, patients will be interviewed by a trained medical officer to assess the adverse effects of trial medication and drug compliance. A full physical examination will be done to assess the adverse effects of trial medication. Compliance to iron chelators will be assessed by direct questioning and by determining the usage by pill counts (for deferasirox and deferiprone) and counting unused vials (for deferoxamine). 2 mL of blood will be collected to an EDTA bottle for full blood count, and another 2 mL will be collected in a plain bottle to assess serum creatinine, aspartate transaminases and alanine transaminases. Measurement of serum ferritin will be done at the enrolment and at 3 months and 6 months. T2\* MRI of the liver and heart, ophthalmological examination and hearing assessment will be done at recruitment and at the completion of 6 months. Safety evaluation includes monthly monitoring of aspartate transaminases, alanine transaminases, serum creatinine, urine analysis for proteinuria and absolute neutrophil count.

A full blood count will be done using the electrical impedance method (Coulter counter). Serum ferritin, serum creatinine, aspartate transaminases and alanine transaminases will be measured in a clinically accredited laboratory. T2\* MRI liver and heart will be done using a clinically accredited MRI machine and reported by a single trained consultant radiologist.

## Outcome measures

### Primary outcome

Reduction in iron overload, as measured by a reduction in the serum ferritin after completion of the treatment, will be the primary outcome measure. Reduction of 500 ng/mL from the baseline value will be defined as response to iron chelator medication.

### Secondary outcomes

Following secondary outcome measures will be assessed:

1. Reduction in liver iron content (LIC) as measured by T2\* MRI of the liver. A 10% reduction in the LIC from the baseline value will be defined as response to iron chelator medication.
2. Reduction in cardiac iron content as measured by T2\* MRI of the heart. A 10% increase in the cardiac T2\* from the baseline value will be defined as response to iron chelator medication.
3. Side effects of trial medication.

## Statistical analysis

Continuous variables with normal distribution will be presented as mean and SD, and those with skewed distribution will be presented as median and IQR. Categorical variables will be presented as frequency and percentages. The mean difference of serum ferritin concentration and liver and cardiac iron content will be compared between intervention and control arms using Student's t-test. The prevalence of individual side effects will be compared using Fisher's exact test. The intention-to-treat analysis will be carried out in IBM SPSS Statistics V.27.0. Statistical significance is set as  $p < 0.05$ .

## Data management and monitoring

All completed anonymised questionnaires and laboratory reports will be stored in locked cupboards with the participant serial number written on individual files. Only the investigators will have access to hard copies. The electronic database will be maintained as a password-protected file.

## Termination of the trial

The trial will be terminated if:

- ▶ New information arises regarding the safety or efficacy of deferasirox, deferiprone or deferoxamine that indicate a change in the known risk/benefit profile of the medications, such that the risk/benefit is no longer acceptable for subjects participating in the trial.
- ▶ Significant violation of good clinical practice that compromises the ability to achieve study objectives or compromises subject safety.

## Patient and public involvement

Patients are neither involved in the design nor the conduct of subsequent steps of the study. The results of the investigation will be available for participants and will be used in the standard management when required.

## Study status

The trial commenced on 1 June 2023 according to the protocol version 1.0, 8 January 2023 and is currently open for recruitment. We have recruited three patients for the trial so far.

## ETHICS AND DISSEMINATION

Ethical approval for the study has been obtained from the Ethics Committee of the Faculty of Medicine, University of Kelaniya (Ref. P/06/02/2023). The trial is registered at the Sri Lanka Clinical Trials Registry (Ref: SLCTR/2023/010). Informed voluntary written consent will be obtained from all participants before recruiting into the study. When the subject is aged between 12 and 18 years, assent will be obtained from a parent or legal guardian in addition to consent from the subjects. Participants will have the right to withdraw from the trial at any point without providing explanations. The trial results

will be disseminated in scientific publications in reputed journals.

## DISCUSSION

$\beta$ -Thalassaemia major is one of the very first genetic diseases of which the pathophysiology and genetic basis were characterised fully.<sup>14</sup> Despite this, it remains an incurable disease in a majority.<sup>15</sup> A small proportion of patients who have suitable donors are cured by allogeneic haematopoietic stem cell transplantation.<sup>16</sup> Several novel pharmacological therapies, including inhibition of ineffective erythropoiesis by activin receptor IIB ligand trap luspatercept and fetal haemoglobin induction by hydroxyurea, have been studied as adjunct therapies.<sup>17-18</sup> Significant advances have been made in genetic-based therapies using gene therapy or genome editing.<sup>19-22</sup> Despite these advances, many patients with transfusion-dependent  $\beta$ -thalassaemia, those who live in low-income and middle-income countries in particular, are managed medically with regular blood transfusions and iron chelation. Although significant improvements are made in the safety of blood transfusions, many patients with transfusion-dependent  $\beta$ -thalassaemia still die prematurely due to complications related to iron overload.<sup>5</sup>

Since human body does not have a physiological mechanism to excrete excess iron and each pack of transfused blood contains approximately 200 mg of iron, patients with transfusion-dependent  $\beta$ -thalassaemia have a positive iron balance constantly. Although limiting the intake of iron rich food and consumption of black tea along with meals reduce the dietary absorption of iron in these patients, achieving a good iron balance heavily relies on the use of iron chelator medication.<sup>7</sup> The three available iron chelators, deferoxamine, deferasirox and deferiprone, have different modes of action and variable efficacy and adverse effect profiles. Deferoxamine is a hexadentate chelator which binds a 1:1 molar ratio to iron. It effectively removes excess iron in the plasma and hepatic iron in the liver cells.<sup>23</sup> The latter iron is excreted via bile and faeces, while the former is excreted via urine. Deferiprone is a bidentate chelator which binds ferric iron 3:1 at low pH.<sup>8</sup> The complex is eliminated in urine. Deferasirox is a tridentate iron-chelating agent that binds iron in a 2:1 ratio. It mainly removes iron from the liver through faeces.<sup>24</sup>

The current guidelines recommend to use monotherapy of a single iron chelator as the first line in patients with transfusion-dependent thalassaemia. When iron overload is high with the use of a single drug, combination therapy with two iron chelators is recommended.<sup>7</sup> Treating iron overload using more than one iron chelator has many benefits. These include better accessibility to various iron pools, better control of non-transferrin bound to iron, better tolerability, improved compliance, reduced myocardial iron and improved cardiac dysfunction in iron-overload cardiomyopathy.<sup>25</sup> Also, combination

therapy is helpful when dose escalation of a single drug is prevented by drug toxicity and adverse effects.

A major obstacle faced by the physicians caring for patients with transfusion-dependent  $\beta$ -thalassaemia is the inability to chelate iron to the optimal levels, even with a combination of two iron chelators. The Thalassaemia International Federation guideline recommends consistently maintaining serum ferritin below 1000 ng/mL in all patients with transfusion-dependent  $\beta$ -thalassaemia in order to minimise iron overload-related complications.<sup>7</sup> However, in a subset of patients, lowering serum ferritin to levels below 1000 ng/mL has been a major challenge despite using two iron chelators at their maximum doses. The only rational approach for these patients would be to combine all three iron chelators, which has not been studied before. The current trial is designed to evaluate the efficacy of this approach for the first time in patients with very high serum ferritin levels.

The main strength of the study is that the efficacy of combination treatment with all three iron chelators is evaluated in a uniform group of patients with transfusion-dependent  $\beta$ -thalassaemia with very high serum ferritin. The study aims to evaluate the outcome using several outcome measures that assess iron overload, including serum ferritin, T2\* MRI of the liver and T2\* MRI of the heart. Thereby, the study would comprehensively evaluate the efficacy of the new combination treatment on the iron burden.

One important limitation of the study is that some participants may have hepatic dysfunction due to iron overload. In these patients, serum ferritin is not considered a reliable marker of iron overload. However, serum ferritin is still the most widely used biomarker of iron load, even among this subset of patients due to limitations in the availability and cost of MRI.<sup>26</sup> Therefore, we believe the results of the study will provide useful insight into the management of severe iron overload in transfusion-dependent  $\beta$ -thalassaemia.

### Author affiliations

<sup>1</sup>Colombo North Teaching Hospital, Ragama, Sri Lanka

<sup>2</sup>Department of Medicine, University of Kelaniya, Kelaniya, Sri Lanka

<sup>3</sup>Department of Paediatrics, University of Kelaniya, Kelaniya, Sri Lanka

<sup>4</sup>Lady Ridgeway Hospital for Children, Colombo, Sri Lanka

<sup>5</sup>Department of Pathology, University of Kelaniya, Kelaniya, Sri Lanka

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#### ORCID iD

Sachith Mettananda <http://orcid.org/0000-0002-0760-0418>

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