

2021

## Luspatercept diminishes the need for red blood cell replacement in transfusion-dependent $\beta$ -thalassemia patients

Joudeh B. Freij

Wayne State University School of Medicine, [joudeh.freij2@med.wayne.edu](mailto:joudeh.freij2@med.wayne.edu)

Follow this and additional works at: <https://digitalcommons.wayne.edu/crp>



Part of the [Congenital, Hereditary, and Neonatal Diseases and Abnormalities Commons](#), [Hematology Commons](#), [Hemic and Lymphatic Diseases Commons](#), [Hepatology Commons](#), [Internal Medicine Commons](#), [Pediatrics Commons](#), and the [Translational Medical Research Commons](#)

---

### Recommended Citation

FREIJ JB. Luspatercept diminishes the need for red blood cell replacement in transfusion-dependent  $\beta$ -thalassemia patients. *Clin. Res. Prac.* May 28 2021;7(1):eP2570. <https://doi.org/10.22237/crp/1622160060>

This Clinical Decision Report is brought to you for free and open access by the Open Access Journals at DigitalCommons@WayneState. It has been accepted for inclusion in Clinical Research in Practice: The Journal of Team Hippocrates by an authorized editor of DigitalCommons@WayneState.

# Luspatercept diminishes the need for red blood cell replacement in transfusion-dependent $\beta$ -thalassemia patients

JOUDEH B. FREIJ, ScM, Wayne State University School of Medicine, [joudeh.freij2@med.wayne.edu](mailto:joudeh.freij2@med.wayne.edu)

**ABSTRACT** A clinical decision report appraising:

Cappellini MD, Viprakasit V, Taher AT, et al. A phase 3 trial of luspatercept in patients with transfusion-dependent  $\beta$ -thalassemia. *N Engl J Med.* 2020;382(13):1219-1231. <https://doi.org/10.1056/NEJMoa1910182>

for a patient with transfusion-dependent beta-thalassemia.

**Keywords:** *beta-thalassemia, luspatercept*

## Clinical-Social Context

Emily Davis [pseudonym] is a 23-year-old woman with a past medical history of transfusion-dependent  $\beta$ -thalassemia major and secondary hemosiderosis. She has received two units of packed red blood cells nearly every four weeks for 20 years. Emily presents to the outpatient pediatric hematology clinic for a scheduled transfusion. She has been coming to this clinic for her care since childhood and has never had any difficulty with her transfusions. Early during her disease, a hematopoietic stem cell transplant was attempted, but an HLA matched donor was never found.

At this visit, Ms. Davis had no complaints and reported that she has been taking her penicillin prophylaxis and deferasirox for iron chelation regularly. She tolerates both medicines well. Ms. Davis has good family support, no difficulties with transportation, and no issues with her insurance. At this visit, she was relaxed and friendly with the staff. She was among people that had been with her during her lifelong journey of wellbeing. Her father was also in attendance and contributed to the positive atmosphere.

Her ferritin level was high at this visit, but the care team was not concerned given her dependence on chronic red blood cell transfusions. Her hemoglobin was 9.7 g/dL; she was transfused with 12cc/kg, for a total of 767 ml, which was typical for her.

As mentioned previously, Ms. Davis did not have any complaints or concerns, but the care team brought to her attention the long-term health consequences of hemosiderosis, including liver failure and other organ involvement that might shorten her life expectancy. This reminded her of the seriousness of her disease. We mentioned a new drug therapy aimed at enhancing her red blood cell maturation, called luspatercept which could potentially decrease the frequency of transfusions.

JOUDEH B. FREIJ, ScM, is an MD candidate at the Wayne State University School of Medicine and a Senior Editor of this Journal.



Ms. Davis seemed receptive because she was aware of the long-term complications of hemosiderosis and the risks inherent in stem cell transplant but wanted to get more information about the novel therapy. Because she was feeling well and any new drug would have potential adverse reactions, she told us, "I need more information." The care team did explain that this medication could reduce her frequency of transfusions, but we were not familiar with the specifics of the medication because of its infrequent use in pediatric populations. We committed to explore the clinical research evidence related to luspatercept and give her more information at her next scheduled appointment.

## Clinical Question

Is there a therapy that is effective at reducing transfusion requirements in patients with  $\beta$ -thalassemia?

## Research Article

Cappellini MD, Viprakasit V, Taher AT, et al. A phase 3 trial of luspatercept in patients with transfusion-dependent  $\beta$ -thalassemia. *N Engl J Med.* 2020;382(13):1219-1231. <https://doi.org/10.1056/NEJMoa1910182><sup>10</sup>

## Description of Related Literature

UpToDate was explored first using the search term "beta thalassemia transfusion." The article on "Management and prognosis of thalassemias" was examined for a basic understanding of therapeutic guidelines. Four key therapies were explained: chronic transfusions, curative hematopoietic stem cell transplant, gene therapy, and novel drug therapies such as luspatercept. The search term "(beta thalassemia[Title/Abstract]) AND ((gene therapy[Title/Abstract]) OR (luspatercept[Title/Abstract])) AND (transfusion[Title/Abstract])" was entered on PubMed and generated 43 results as of October 2020. Of the results, three of the 43 were clinical trials. The remaining 40 consisted of 31 reviews (and were excluded from analysis), a pharmacokinetic study of luspatercept (also excluded from the study), a case report of a trial protocol plan for gene therapy that has no data (also excluded), and a paper about the clinical guidelines of beta-thalassemia management (was excluded). Six additional studies (two studies examining epigenetics of the globin gene and four studies examining the use of pluripotent stem cells and the efficacy on using different vectors in patients with  $\beta$ -thalassemia) were also found.<sup>1-6</sup> However, these were ultimately not used for answering the clinical question addressed as they only looked at experimental samples from patients, were not randomized, and were not comparing an experimental drug to a placebo or gold standard of therapy. An additional search using Google Scholar was performed by entering the title of the paper chosen for critical appraisal, and then selecting "Related Articles" which resulted in 101 articles. Titles were scanned and all were excluded, as they did not address  $\beta$ -thalassemia and transfusions, except for one additional clinical trial.

The study by Thompson et al. consists of two phase 1/2 non-randomized, open-label, single dose clinical trials examining the efficacy and safety of gene therapy in treating patients with transfusion-dependent  $\beta$ -thalassemia.<sup>7</sup> The trial enrolled 22 patients in total. Hematopoietic stem cells were first harvested from recruited patients. Patients then underwent myeloablation with busulfan prior to injection of autologous hematopoietic stem cells transduced with a lentiviral vector containing normal  $\beta$ -globin gene. By the end of 3 years of follow up, 13 patients no longer required transfusions after the engraftment, but these patients had a non- $\beta^0/\beta^0$  genotype, i.e. not  $\beta$ -thalassemia major. Of the nine patients that did have  $\beta$ -thalassemia major, six had a 74% reduction in transfusion frequency and a 73% reduction in the volume received. Although this study showed a significant reduction in overall transfusion requirement in  $\beta$ -thalassemia major patients, there was only a small number of patients that fit a similar picture to Ms. Davis. Although autologous stem cell transplants have fewer side effects than allogenic stem cell transplant, myeloablation is still a required process to enhance success of the engraftment, which comes with its own complications. Thus, a less invasive therapy was explored.

The study by Cappellini et al. in 2019 was a phase 2 clinical trial of sotatercept examining dosage requirements for effective treatment.<sup>8</sup> The inclusion criteria were patients  $\geq 18$  years old who had either transfusion dependent or non-transfusion dependent  $\beta$ -thalassemia. These patients were treated with increasing doses of sotatercept and a primary end point of a reduction in transfusion burden of at least 20% sustained over at least 24 weeks was determined. The study recruited a total of 46 patients, 16 of



FREIJ JB. Luspatercept diminishes the need for red blood cell replacement in transfusion-dependent  $\beta$ -thalassemia patients. *Clin. Res. Prac.* May 28 2021;7(1):eP2570.  
<https://doi.org/10.22237/crp/1622160060>

whom were transfusion dependent and 30 of whom were not transfusion dependent, and the mean treatment duration was about 19 months. Progressive dose escalation occurred, and patients received at least 2 doses of sotatercept. The study did conclude that for 10 of the transfusion dependent patients there was at least a 20% reduction in transfusion burden. Although this study did show similar results to luspatercept, there are several points that make this article inferior to the phase three trial. This study focused on determining appropriate doses for sotatercept, determined major adverse effects of the drug, was a small study, and did not compare medication effects to a placebo.

The study by Piga et al. was a phase 2 clinical trial of the chosen study, and was done to determine the appropriate dose of luspatercept that was needed to have an effect on reduction of transfusion requirements.<sup>9</sup> As there is a phase 3 clinical trial on the efficacy of luspatercept versus placebo, this study was not chosen to answer the clinical question relating to Ms. Davis.

The article chosen for critical appraisal was by Cappellini et al., a randomized, double-blinded, phase 3 clinical trial comparing the efficacy of reducing transfusion requirements in  $\beta$ -thalassemia patients treated with luspatercept versus placebo.<sup>10</sup> This study recruited 336 patients with either  $\beta$ -thalassemia or hemoglobin-E (HgE)  $\beta$ -thalassemia who required transfusions of 6-20 packed red blood cell (pRBC) units over a 24-week period. The study concluded that there was a clinically and statistically significant difference in transfusion requirements in the luspatercept group as compared to placebo. This study was ultimately chosen over the study by Thompson et al to answer the clinical question because Ms. Davis fit within the inclusion criteria, the study was a phase 3 randomized clinical trial, and treatment with luspatercept only required a subcutaneous injection and not myeloablative therapy to show an improvement in transfusion requirements.

Based on Strength of Recommendation Taxonomy (SORT) criteria [cite], the above body of evidence would be a grade B, given that there are limited clinical trials examining  $\beta$ -thalassemia and improving transfusion dependence.<sup>11</sup>

## Critical Appraisal

The study by Cappellini et al. is a double-blinded, randomized phase 3 controlled trial that recruited patients from 65 sites in 15 countries in North America, Europe, Africa, the Middle East, and Asia. A total of 336 patients with either  $\beta$ -thalassemia or HgE  $\beta$ -thalassemia were randomized in a 2:1 ratio to receive luspatercept (224 patients) or placebo (normal saline), with an intention-to-treat analysis. Inclusion criteria for the study were patients 18 - 60 years old, had a confirmed diagnosis of  $\beta$ -thalassemia or HgE  $\beta$ -thalassemia, and were regularly transfused with 6-20 packed red blood cell (pRBC) units over a 24-week period. Exclusion criteria included patients with significant organ damage (heart failure, liver disease, lung disease, or kidney disease), medical conditions that would not allow them to participate in the study, had received luspatercept or sotatercept prior to the study, and several others listed in the Supplemental materials of the article. These exclusion criteria do suggest that there is some selection bias, particularly that very sick and chronically ill patients were not included, and thus the benefit that this drug may have on reducing iron levels and transfusion requirements in these patients cannot be determined. Yet, randomization ensures that each treatment group will be equally represented by the population meeting the inclusion criteria. Given these points, Ms. Davis meets the inclusion criteria and did not have any of the exclusion criteria, thus making her eligible for participation in this study.

Randomization of the study was successful, as an equal representation for each of the subgroups, as shown in Table 1 of the article, was present, thus reducing any confounding factors. The demographic information of the patients in the study also match with Ms. Davis (e.g. age range of 18 – 66, 58% female, a median Hgb level of 9.3 g/dl, transfusion burden range of 6 – 24 over a 24-week period). Luspatercept, given at a dose of 1.00 mg/kg and titrated up to 1.25 mg/kg, and placebo were given every 21 days for up to 48 weeks. Although luspatercept was not compared to a “gold standard” therapy, the goal of the study was to determine if patients could have a reduced transfusion need (the “gold standard” therapy for  $\beta$ -thalassemia).

The primary outcome measured was a reduction in transfusion burden by at least 33% from baseline during weeks 13 to 24 and a reduction of at least 2 pRBC units during the interval. Secondary endpoints measured included a 33% reduction in transfusion burden plus a reduction of at least 2 pRBC units during weeks 37 to 48, a 50% reduction in transfusion burden plus a reduction of at least 2 pRBC units during weeks 13 to 24, a 50% reduction in transfusion burden plus a reduction of at least 2 pRBC units during weeks 37 to 48, and a reduction in transfusion of 33% or 50% plus a reduction of at least 2 pRBC units during any 12- or 24-week interval. Additional laboratory values of ferritin level, liver iron content, change in hemoglobin level, and myocardial iron deposition were also measured.



This study found that 21.5% (48/224) of patients treated with luspatercept had a 33% reduction in transfusion burden in weeks 13 - 24 versus 4.5% (5/112) of patients given placebo, with an odds ratio of 5.79 ( $p < 0.001$ ). Given this odds ratio for the primary endpoint of the study, the number-needed-to-treat is 6. All secondary endpoint outcomes assessing transfusion burden were reported and reported that there was a statistically significant difference between luspatercept and placebo. Other secondary endpoints included examining the duration and time of erythroid response, change in hemoglobin level from baseline, serum ferritin level, liver iron concentration at week 48, myocardial iron deposition, and adverse events were reported in either the article or the supplemental material, and all showed that luspatercept was superior to placebo. Particularly, 70.5% of patients (158) treated with luspatercept had at least a 33% reduction in transfusion burden during any 12-week interval, while there were only 29.5% of the placebo group (34). Furthermore, patients treated with luspatercept had an erythroid response after 12 days in those with a 33% reduction or 24.5 days in those with a 50% reduction. Additionally, erythroid response durations lasted for an average of 104 days for patients with a 33% reduction (158 patients) or 98 days for patients with a 50% reduction in transfusion burden (90 patients). Regarding serum ferritin levels, there was a mean difference of  $-348 \mu\text{g/L}$  (95% CI  $-517$  to  $-179$ ) when comparing patients on luspatercept versus placebo. However, the authors report that although this value was statistically significant, there were no clinical differences in liver iron concentration or myocardial iron deposition, which was reported in the supplemental data section. 96% of patients in the luspatercept group experienced adverse events, with the most common by far being bone pain that was well controlled with analgesics. The study reported that 48 patients from the luspatercept group and 24 patients from the placebo group dropped out of the study.

Strengths of this study include the fact that patients were recruited from several centers around the globe, which adds to the external validity of the study's conclusions. Also, blinding both the patients and investigators limits the likelihood that biases, such as selection and accidental biases, will have a major impact on the study results. Additionally, this is an intention-to-treat analysis, which allows for accurate conclusions to be made from the data presented and limits attrition bias that would be present, which means that even though patients dropped out from the study, they were still analyzed according to the study arm they were randomized to. Treating the patients with two doses of luspatercept that were both found to be safe, allows for the authors to determine if there is a dose of luspatercept that results in better outcomes regarding reduction in transfusion burden. There is no evidence of publication bias as this study is registered on [clinicaltrials.gov](https://clinicaltrials.gov) (NCT02604433). Funding bias is likely absent as the sponsors (Celgene and Accerlon Pharm) were involved in the study but worked with a steering committee and received advice from regulatory agencies.

Although several strengths are present in this study, some weaknesses are present. The authors only carry out the treatment for about 1 year, and although patients could undergo further follow-up, the duration was not specified. It is possible that even more of a difference could have been observed in both the primary and secondary endpoints had the study lasted longer than a year. It is also possible that the secondary endpoints examining the complications of iron-overload could have showed more of a clinical significance. Additionally, given that there are three major iron chelators each with different mechanisms of action and side effects, differences in iron levels may be due to different iron chelators.<sup>12</sup> The authors did not state which iron chelators were used and simply report that best practices for the treatment of  $\beta$ -thalassemia will be followed local practices. This is a multinational study and it was not stated what differences between various countries are regarding when to initiate transfusions or what iron chelators are used. These points should be standardized to ensure that the patients are more homogenous. Additionally, the authors mention that no clinically significant difference in liver iron concentration and myocardial iron deposition were noted. This finding weakens the clinical utility of luspatercept. Iron liver concentrations and myocardial iron deposition are significant indicators of complications of hemosiderosis, and the goal of reducing transfusion frequency is to reduce the likelihood of progressing to severe complications of hemosiderosis. The authors do address this point in the discussion but did not present a clear reason for no clinically significant difference.

Based on the SORT criteria, as this study is a randomized controlled, double-blinded study, it would have a Level 1 quality of study.<sup>11</sup>

## Clinical Application

Ms. Davis was a young female with transfusion dependent  $\beta$ -thalassemia and iron chelation therapy for several years, who failed to find a matched HLA donor for stem cell transplant. Although she has not had any major complaints throughout her multiple visits to the Pediatric Hematology/Oncology clinic, the care team decided to bring to her attention a novel therapy that could reduce her transfusions requirements.



The study by Cappellini et al in 2020 showed that patients with transfusion dependent can have a reduction in transfusion burden by at least 33% and some even had a reduction of 50%. Although Ms. Davis did not have any current complications of iron overload, she will always be at risk for developing these complications and providing her with the opportunity to decrease her need for transfusions by 33% and possibly up to 50%, could significantly help prevent the progression of hemosiderosis and reduce her need for frequent transfusions, reducing her need to constantly be on iron-chelation therapy. The conclusions from this study are very applicable, given that she matches many of the patient demographics stated in the paper. Furthermore, given the fact that this study was conducted in multiple different countries, external validity is also strong, which only supports the application of this study to Ms. Davis and potentially other patients in a similar situation. Although this treatment may not completely cure her  $\beta$ -thalassemia, it is the only option that will provide her with the best outcome with minimal significant adverse side effects. Gene therapy and stem cell transplant, while beneficial, both come with many complications that could impact the day-to-day life of Ms. Davis, which currently is not an issue. Luspatercept treatment, on the other hand, appears to be a safe, effective, and easy treatment to help reduce her transfusion needs and not cause any significant side-effects that could worsen her day-to-day activities. We generated documentation to provide this information to Ms. Davis at her next routinely scheduled appointment. At her next routinely scheduled appointment, we aimed to summarize the literature search, stress the results of the study, and state the benefit that luspatercept could have in reducing her transfusion burden.

## New Knowledge Related to Clinical Decision Science

Specialized doctors that care for patients with relatively rare chronic illnesses develop emotional attachments within the doctor patient relationship. This level of trust allows for medical management discussions related to chronic disease progression and mortality. To maintain that trust, doctors must commit to self-education and sharing with patients as they face existential decisions together. This provides them with a unique opportunity to discuss the literature regarding new and alternative approaches to medical management and allows them to tailor the management based on what both the physician and patient agree upon. This concept of making care “patient-centered” and committing to explore clinical research for a specific patient situation to guide management and decisions with the patient is the goal of “point of care clinical research evidence.”<sup>13</sup>

## Conflict Of Interest Statement

The author declares no conflicts of interest.

## References

1. Tubsubwan A, Abed S, Deichmann A, et al. Parallel assessment of globin lentiviral transfer in induced pluripotent stem cells and adult hematopoietic stem cells derived from the same transplanted  $\beta$ -thalassemia patient. *Stem Cells.* 2013;31(9):1785-1794. <https://doi.org/10.1002/stem.1436>
2. Malik P, Arumugam PI, Yee JK, Puthenveetil G. Successful correction of the human Cooley’s anemia  $\beta$ -thalassemia major phenotype using a lentiviral vector flanked by the chicken hypersensitive site 4 chromatin insulator. *Ann N Y Acad of Sci.* 2005;1054(1):238-249. <https://doi.org/10.1196/annals.1345.030>
3. Puthenveetil G, Scholes J, Carbonell D, et al. Successful correction of the human  $\beta$ -thalassemia major phenotype using a lentiviral vector. *Blood.* 2004;104(12):3445-3453. <https://doi.org/10.1182/blood-2004-04-1427>
4. Frittoli MC, Biral E, Cappelli B, et al. Bone marrow as a source of hematopoietic stem cells for human gene therapy of  $\beta$ -thalassemia. *Hum Gene Ther.* 2011;22(4):507-513. <https://doi.org/10.1089/hum.2010.045>
5. Paciaroni K, Lucarelli G, Martelli F, et al. Transfusion-independent  $\beta(0)$ -thalassemia after bone marrow transplantation failure: proposed involvement of high parental HbF and an epigenetic mechanism. *Am J Blood Res.* 2014;4(1):27-32.
6. Dong A, Ghiaccio V, Motta I, et al. 2’-O-methoxyethyl splice-switching oligos correct splicing from IVS2-745  $\beta$ -thalassemia patient cells restoring HbA production and chain rebalance. *Haematologica.* 2020;105:haematol.2019.226852. <https://doi.org/10.3324/haematol.2019.226852>



FREIJ JB. Luspatercept diminishes the need for red blood cell replacement in transfusion-dependent  $\beta$ -thalassemia patients. *Clin. Res. Prac.* May 28 2021;7(1):eP2570.  
<https://doi.org/10.22237/crp/1622160060>

7. Thompson AA, Walters MC, Kwiatkowski J, et al. Gene therapy in patients with transfusion-dependent  $\beta$ -thalassemia. *N Engl J Med.* 2018;378(16):1479-1493. <https://doi.org/10.1056/nejmoa1705342>
8. Cappellini MD, Porter J, Origa R, et al. Sotatercept, a novel transforming growth factor  $\beta$  ligand trap, improves anemia in  $\beta$ -thalassemia: A phase II, open-label, dose-finding study. *Haematologica.* 2019;104(3):477-484. <https://doi.org/10.3324/haematol.2018.198887>
9. Piga A, Perrotta S, Gamberini MR, et al. Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with  $\beta$ -thalassemia. *Blood.* 2019;133(12):1279-1289. <https://doi.org/10.1182/blood-2018-10-879247>
10. Cappellini MD, Viprakasit V, Taher AT, et al. A phase 3 trial of luspatercept in patients with transfusion-dependent  $\beta$ -thalassemia. *N Engl J Med.* 2020;382(13):1219-1231. <https://doi.org/10.1056/nejmoa1910182>
11. Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): A patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Pract.* 2004;17(1):59-67. <https://doi.org/10.3122/jabfm.17.1.59>
12. Choudhry VP. Thalassemia minor and major: current management. *Indian J Pediatr.* 2017;84(8):607-611. <https://doi.org/10.1007/s12098-017-2325-1>
13. Meza JP, Yee N. Editorial: Clinical practice can save evidence-based medicine from itself. *Clin Res Pract.* 2018;4(2):eP1833. <https://doi.org/10.22237/crp/1535414460>

