

## LUSPATERCEPT – A better strategy for thalassemia?

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*Dear Editor,* Amongst the cluster of diseases widespread in Pakistan,  $\beta$ -thalassemia is one of the most common genetic disorders. More than 5,000 children in Pakistan suffer from  $\beta$ -thalassemia annually, with a carrier rate of 5-8 percent.<sup>1</sup> The principal cause for the high prevalence in Pakistan is consanguinity. Regular blood transfusions and iron chelation are the focal treatment options for  $\beta$ -thalassemia patients, while bone marrow transplantation (BMT) has been established as the only definitive cure.<sup>1</sup>

Luspatercept and Sotatercept are specific activin receptor fusion compounds that suppress the TGF- $\beta$  pathway for negative regulation of RBC maturation.<sup>2</sup> The binding of activin receptor ligands reduces abnormal Smad 2/3 signalling and prevents apoptosis and cell-cycle arrest in erythroblasts, thus promoting late-stage differentiation.<sup>2,3</sup> Luspatercept provides a fresh prospect to treat diseases that involve inadequate RBC differentiation, leading to an increased number of immature erythroid precursors in blood.  $\beta$ -thalassemia and myelodysplastic syndromes (MDS) are the current major targets. It is not indicated as RBC substitute in acutely anaemic patients.

Luspatercept use concluded increased haemoglobin levels in a Phase 1 study involving healthy postmenopausal women and decreased transfusion burden by 20% in 12 weeks in a Phase 2 study.<sup>3,4</sup> The U.S. Food and Drug Administration (FDA) approved the drug in Nov. 2019 for adult patients with  $\beta$ -thalassemia who needed regular RBC transfusions.<sup>5</sup> Efficacy was evaluated in a multicenter BELIEVE trial conducted at 65 different locations across 15 countries.<sup>6</sup> A group of 224 patients were randomly given the drug and compared to 112 that received the placebo. The reduction in transfusion burden was significantly higher in the Luspatercept group.<sup>6</sup> The drug's major side effects included headache, arthralgia, hypertension and

hyperuricaemia, while thrombo-embolic events (3.6%) only occurred in patients who had undergone a splenectomy while having a concomitant risk factor.

In Pakistan, the significant burden of frequent blood transfusions has a massive impact on individuals and the health care system. The overwhelming cases of  $\beta$ -thalassemia in Pakistan could pave the way for this drug to make a significant difference. It could lead the way to a more independent life, markedly reducing the frequency of transfusions and the complications associated with it. The support of the government and big pharmaceuticals can open the doors for conducting clinical trials to evaluate the efficacy and cost feasibility of Luspatercept in Pakistan.

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### References

1. Jamil B. Clinical features, diagnosis and management of COVID-19 patients in the outdoor setting. *J Pak Med Assoc* 2020; 70(Suppl 3): s52-5.
2. Suragani R, Cadena S, Cawley S, Sako D, Mitchell D, LiR, et al. Transforming growth factor- $\beta$  superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. *Nat Med* 2014; 20: 408-14.
3. Attie KM, Allison MJ, McClure T, Boyd IE, Wilson DM, Pearsall AE, et al. A phase 1 study of ACE-536, a regulator of erythroid differentiation, in healthy volunteers. *Am J Hematol* 2014; 89: 766-70.
4. Piga A, Perrotta S, Gamberini MR, Voskaridou E, Melpignano A, Filosa A, et al. Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with  $\beta$ -thalassemia. *Blood* 2019; 133: 1279-89.
5. Wang W, Sun Q. Novel targeted drugs approved by the NMPA and FDA in 2019. *Signal Transduct Target Ther* 2020; 5: 65.
6. Cappellini MD, Viprakasit V, Taher AT, Georgiev P, Kuo KHM, Coates T, et al. A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent  $\beta$ -Thalassemia. *N Engl J Med* 2020; 382: 1219-31.

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