Mediterranean Journal of Hematology and Infectious Diseases

Scientific Letters

Luspatercept Treatment in a β-Thalassemia Patient with Pulmonary Arterial Hypertension: A Case Report

Keywords: β-thalassemia; Luspatercept; Pulmonary arterial hypertension treatment.

Published: September 01, 2025 **Received: June 11, 2025** **Accepted: August 11, 2025**

Citation: Yang B., Liu D., Yang C., Zhou Y., Liao G., Huang J., Li Y., Tang Y., Yin X. Luspatercept treatment in a β-thalassemia patient with pulmonary arterial hypertension: a case report. Mediterr J Hematol Infect Dis 2025, 17(1): e2025059, DOI: http://dx.doi.org/10.4084/MJHID.2025.059

To the editor.

Thalassemias are a group of inherited hemoglobinopathies caused by mutations in the α-globin or β-globin gene clusters, leading to impaired hemoglobin synthesis and imbalanced globin chain production, which have a significant prevalence in many countries, including China. β-thalassemia is characterized by an excess of α-globin chains and insufficient β-globin, leading to ineffective erythropoiesis and hemolysis. This results in chronic hemolytic anemia, ineffective erythropoiesis, and complications including iron overload, bone deformities, and growth impairment.[1] Based on transfusion dependence, β-thalassemia is classified into two clinical phenotypes: transfusion-dependent thalassemia (TDT), which requires lifelong regular red blood cell transfusions for survival, and non-transfusion-dependent thalassemia (NTDT), which does not require regular transfusions but may need occasional transfusions due to infections or stressors. TDT is predominantly associated with iron overload (affecting >80% of adults), endocrine disorders (e.g., hypogonadism, diabetes; 40-60% prevalence), and transfusion-transmitted infections, driven by chronic transfusions. Cardiac iron overload remains a leading cause of mortality. NTDT more frequently involves extramedullary hematopoiesis (≥50% of patients), thrombotic events (e.g., stroke; 10-30%), leg ulcers, and pulmonary hypertension (PAH), primarily due to chronic hemolysis and hypercoagulability. Splenectomy further elevates thrombosis risk. PAH represents a spectrum of diseases increasingly recognized as a major source of morbidity and mortality across various conditions. Elevated pulmonary arterial pressure (PAP) exerts strain on the right ventricle, which can ultimately progress to right ventricular failure and death.[2] Moreover, the development of PAH in thalassemia is known to result from multifactorial mechanisms, including chronic hemolysis, iron overload, hypercoagulability, and alterations in circulating cells following splenectomy. The prevalence of PAH in β-thalassemia patients, as confirmed on right heart catheterization, was 2.1%,[3] with higher rates observed in NTDT and post-splenectomy patients. Data on the use of pulmonary vasodilators in β-thalassemia are limited. The 4-year mortality rate of PAH in β-thalassemia is as high as 54.2%.[4] Luspatercept has been shown to increase hemoglobin levels in β-thalassemia by promoting the differentiation and maturation of late-stage red blood cell precursors.[5] Given the poor prognosis and treatment challenges associated with PAH in β-thalassemia, this paper reports on the impact of luspatercept treatment on a patient with β-thalassemia and PAH.

Case. We present the case of a 33-year-old Chinese man diagnosed with β-thalassemia at the age of 1. He has been receiving intermittent transfusion therapy and regular iron-chelating therapy since the age of 30. His genotype is CD17(A⟩T)/βE, and he underwent splenectomy at age 11. Due to limited blood resource availability in the local healthcare system during the early treatment phase, which constrained consistent transfusion access, he received occasional transfusions every 6-10 months to maintain his hemoglobin levels at 70-80 g/L. From age 30, he also received daily iron-chelating therapy using Deferasirox (30 mg/kg/d). He was considered a NTDT patient.

In February 2022, at age 31, he experienced chest discomfort and shortness of breath following physical activity, which resolved with rest. He was admitted to a cardiovascular hospital where initial tests revealed the following: white blood cell count (WBC) 11.29×10^9/L, hemoglobin (Hb) 75 g/L, platelet count (PLT) 671×10^9/L, nucleated red blood cell count (NRBC) 11.03×10^9/L, serum ferritin (SF) 1238.7 ng/mL, prothrombin time (PT) 14.8 s, and D-dimer 0.33 μg/mL. Liver function tests showed total bilirubin (TBil) 102.12 μmol/L, indirect bilirubin (IBil) 80.95

Table 1. Right heart catheterization results.

	Basic Complications	After Inhalation of Vantavir(20μg)
Haemodynamics		
RAP, mmHg	13/11/11	12/10/9
RVP, mmHg	60/22/25	57/16/19
PAP, mmHg	57/31/43	54/30/40
PAWP, mmHg	13	12
PVR, Wood U	3.24	3.37
TPR, Wood U	4.64	4.82
SVR, Wood U	6.90	11.10

RAP: Right Atrial Pressure; RVP: Right Ventricular Pressure; PAP: Pulmonary Artery Pressure; PAWP: Pulmonary Artery Wedge Pressure; PVR: Pulmonary Vascular Resistance; TPR: Total Pulmonary Resistance; SVR: Systemic Vascular Resistance

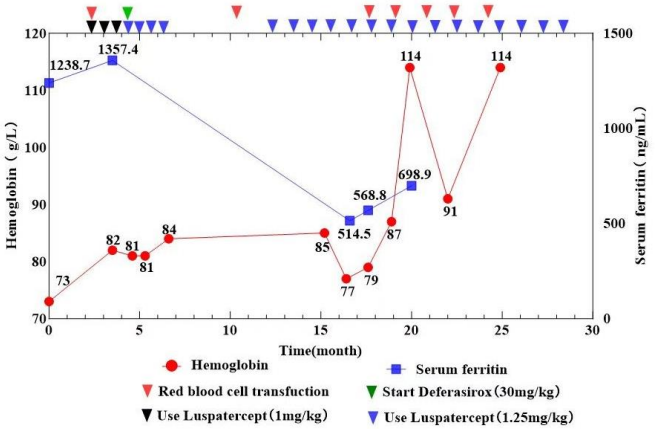

Figure 1. The change in hemoglobin and serum ferritin after Luspatercept. In July 2022, the patient began receiving Luspatercept at 1mg/kg every 21 days, and after two months, the dose was adjusted to 1.25mg/kg every 21 days. He received daily iron-chelating therapy using Deferasirox (30 mg/kg/d) from September 2022. He received occasional transfusion therapy every 6-10 months during the early treatment phase, and he has maintained a bimonthly transfusion therapy since September 2023.

μmol/L, and lactic dehydrogenase (LDH) 174 U/L. Echocardiography demonstrated mild tricuspid regurgitation, with a tricuspid regurgitation jet velocity (TRV) of 3.4 m/s and an estimated pulmonary artery systolic pressure of 51 mmHg. Pulmonary function tests showed moderate to severe restrictive ventilatory dysfunction; small airway dysfunction; pulmonary diffusing capacity was moderately decreased, and bronchodilation tests were negative. Contrast-enhanced CT of the pulmonary arteries results showed no evidence of embolism in the segmental and proximal pulmonary arteries, and pulmonary artery dilatation is present. Right heart catheterization (**Table 1**) results showed pulmonary artery pressure (PAP) 57/31/43mmHg, pulmonary vascular resistance (PVR) 3.24 Wood U, and pulmonary artery wedge pressure (PAWP) 13mmHg, which indicated PAP and PVR, with a decreased PAWP, suggesting precapillary pulmonary hypertension. His 6-minute walk test (6MWT) recorded 356 meters.

The patient was diagnosed with PAH and was treated with spironolactone for diuresis and digoxin to enhance cardiac function. Additionally, he received low-dose Riociguat (0.5 mg three times daily) to lower pulmonary artery pressure due to the following treatment-emergent headache. After approximately three months on this regimen, his condition showed no significant improvement. In June 2022, the 6MWT was 350 meters. Echocardiography demonstrated mild tricuspid regurgitation, with a TRV of 3.3 m/s and an estimated pulmonary artery systolic pressure of 49 mmHg.

Luspatercept was approved by China's National Medical Products Administration (NMPA) in 2022 for the treatment of adult patients with β-thalassemia who require regular red blood cell transfusions and do not have contraindication in PAH. Then, the patient began receiving Luspatercept at 1mg/kg every 21 days, and after two months, the dose was adjusted to 1.25mg/kg every 21 days. In July 2022, the magnetic resonance imaging (MRI) results indicated Cardiac T2* MRI: 46.89 ms (normal >20 ms); Liver iron concentration: >14 mg/g dw (Severe overload). **Figures 1** show the changes in serum ferritin and hemoglobin levels following the Luspatercept therapy. **Figures 2** show the changes in the Echocardiogram before and after treatment with Luspatercept. The patient reported improved chest discomfort and shortness of breath after the second dose of Luspatercept. 2 months after receiving Luspatercept, he followed up with the hematological index (**Table 2**), indicating increased HB, decreased SF, and improved hemolysis markers (bilirubin and NRBC). At 14 and 21 months of follow-up, improvements were maintained, and echocardiography showed normal TRV (**Table 2**). After improving significantly, the patient enhanced their motivation to seek further treatment. This improvement in compliance, combined with the family's efforts to identify alternative blood supply sources, eventually enabled more consistent transfusions. In April 2024, after detailed counseling, the patient made an informed decision to discontinue luspatercept treatment in order to enroll in a potentially curative gene therapy clinical trial, requiring ≥8-week washout of erythroid-active

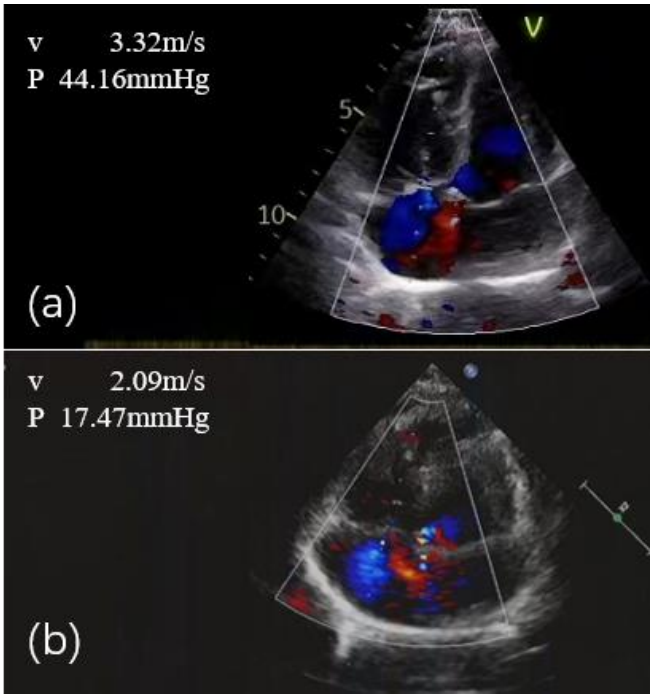

Figure 2. Patient's Echocardiogram before and follow-up after treatment with Luspatercept. (a) Presented the patient's Echocardiogram prior to Luspatercept treatment, showing a tricuspid regurgitation jet velocity of 3.32 m/s, a tricuspid valve pressure gradient of 44.16 mmHg, and an estimated pulmonary artery systolic pressure of 49 mmHg; (b) Presented the patient's Echocardiogram 21 months after Luspatercept treatment, showing a tricuspid regurgitation jet velocity of 2.09 m/s, a tricuspid valve pressure gradient of 17.47 mmHg, and an estimated pulmonary artery systolic pressure of 17 mmHg.

agents. An echocardiogram at the cardiovascular hospital in August 2024 revealed mild tricuspid regurgitation, with a TRV of 3 m/s and an estimated pulmonary artery systolic pressure of 41 mmHg.

Discussion. Based on the patient's Echocardiogram and Contrast-enhanced CT of the pulmonary arteries, pulmonary hypertension secondary to left heart disease, pulmonary hypertension associated with hypoxia, or pulmonary artery obstruction due to lung disease has been excluded. PAH secondary to β-thalassemia is classified under Group 5 pulmonary hypertension (PH), encompassing disorders with multifactorial and incompletely understood mechanisms.[6] The presented case highlights a splenectomized patient with β-thalassemia exhibiting hallmark features of chronic hemolysis, iron overload, platelet activation, and hypercoagulability - all recognized risk factors for PAH progression.

Conventional management of β-thalassemia-associated PAH centers on transfusion regimens, iron chelation therapy, and supportive measures such as oxygen supplementation, anticoagulation, and cardiac function optimization.[7] According to current ESC/ERS PH Guidelines,[8] Sildenafil, bosentan, and other similar drugs are primarily indicated for pulmonary arterial hypertension (Group 1). However, no prospective studies have confirmed their efficacy in treating pulmonary arterial hypertension caused by thalassemia (Group 5). Despite these interventions, pulmonary vasodilators - including phosphodiesterase type 5 inhibitors (PDE-5i), endothelin receptor antagonists, and the soluble guanylate cyclase stimulator riociguat - demonstrated limited efficacy and unfavorable adverse effect profiles in this patient.[7] Notably, three months of low-dose riociguat failed to ameliorate symptoms or objective measures of PAH.

The 1.25 mg/kg dose of Luspatercept elicited a hemoglobin elevation of approaching 10 g/L, confirming its therapeutic efficacy for anemia management.[9] Intriguingly, concurrent enhancements in 6-minute walk test (6MWT) performance and tricuspid regurgitant velocity (TRV) on echocardiography suggested a rapid reduction in pulmonary vascular resistance. Discontinuation of luspatercept precipitated increased transfusion requirements and recrudescence of pulmonary hypertension, underscoring its therapeutic dependency. Hematologic profiling revealed diminished nucleated red blood cell (NRBC) counts post-treatment, indicative of attenuated ineffective erythropoiesis - a finding potentially linked to PAH mitigation, though mechanistic clarity remains elusive. We acknowledge that this confounding factor (concurrent transfusions) may complicate the interpretation of luspatercept's isolated effects on PAH. However, the temporal association between luspatercept initiation and symptomatic improvement (prior to transfusion intensification) suggests a potential role of the drug, warranting further investigation in controlled settings.

In chronic hemolytic anemia, PAH pathogenesis is driven by nitric oxide (NO) depletion due to free hemoglobin-mediated scavenging, compounded by L-arginine metabolic dysregulation, endothelial dysfunction, and elevated endothelin-1 levels.[10] The phase 3 COMMANDS trial[11] further supports luspatercept's cardioprotective role, demonstrating reduced NT-proBNP levels, likely mediated via TGF- β signaling suppression, apoptotic pathway modulation, and downregulation of pro-inflammatory mediators.[12,13] These effects may synergistically enhance NO bioavailability, offering a plausible pathway for PAH alleviation. Meantime, a phase II, open-label study of sotatercept revealed that sotatercept reduced transfusion requirements in TDT patients.[14] By sequestering SMAD2/3 pathway ligands (e.g., activins, growth differentiation factors), sotatercept restores balance between pro-proliferative and anti-proliferative signaling in the pulmonary vasculature.[15] Its efficacy in PAH is evidenced by a phase 3 trial showing superior 6MWT outcomes versus placebo ($p<0.001$).[16] As a similar agent to luspatercept,[17] which has demonstrated effectiveness in treating PAH in thalassemia in this case,

Table 2. Patient's data before and follow-up after treatment with Luspatercept.

	Baseline	3 months after Riociguat (before Luspatercept)	2 months after Luspatercept	14 months after Luspatercept	21 months after Luspatercept	5 months after discontinuing Luspatercept
Symptom	Chest discomfort, shortness of breath	No improvement	Improvement	A marked improvement	As before	As before
Interval transfusions	7 months	7 months	7 months	7 months	2 months	2 months
NYHA class	III	III	II	I	I	I
6 MWT	356m	350m	420m	502m	510m	430m
Hematological index						
Hb, g/L	75	80	81	85	88	83
PLT, ×10^9/L	671	808	815	907	828	709
Ret, ×10^9/L	386.8		402.4	642.6		448.20
NRBC, ×10^9/L		46.795	24.01	38.17		12.53
TBil, mmol/L	102.12	83.2	80.5	77.3	77.6	74.8
IBil, mmol/L	80.95	65.9	64.2	64.2	65	63.5
LDH, U/L	174	144		168		136
Ferritin, ng/mL	1238.7	1357.4	1076.4	568.8	425	390.4
NT-pro BNP, pg/mL	134.6	136.9				
Echocardiogram						
TRV	3.4m/s	3.3m/s		Not seen	2.09m/s	3m/s
Estimated PAP	51mmHg	49mmHg		-	17mmHg	41mmHg
LVEDD	52mm	50mm		49mm	48mm	47mm
RVED	35mm	37mm		30mm	29mm	31mm
EF	58%	68%		62%	66%	64%

NYHA class: New York Heart Association functional class; 6 MWT: 6-minute walk test; Hb: hemoglobin; PLT: platelet count; Ret: reticulocyte; NRBC: nucleated red blood cell count; TBil: total bilirubin; IBil: indirect bilirubin; LDH: lactic dehydrogenase; NT-pro BNP: N-terminal B-type natriuretic peptide; TRV: tricuspid regurgitation jet velocity; Estimated PAP: estimated pulmonary artery systolic pressure; LVEDD: Left ventricular end-diastolic diameter; RVED: Right ventricular basal diameter; EF: ejection function.

the potential efficacy of sotatercept in PAH in thalassemia (classified under Group 5) is worth exploring.

β-thalassemia-related PAH confers significant mortality risk, yet pharmacologic interventions - particularly those achieving >25% hemodynamic improvement - may attenuate this burden.[4] In this case, luspatercept yielded dual hematologic and cardiopulmonary benefits, suggesting a novel role in modulating pulmonary vascular resistance. With symptomatic relief improving compliance, the patient could maintain transfusion regimens more effectively, thereby meeting the eligibility criteria for experimental gene therapy as a potential cure. While preliminary, these observations warrant rigorous investigation to delineate luspatercept's pleiotropic effects and optimize therapeutic strategies in this high-risk population. At the same time, based on the role of microthrombotic events in the evolution of PAH in thalassemia, an increase in the thrombotic risk may become evident in the long-term use of luspatercept and must be promptly recognized.

Author Contributions. Xiaolin Yin, Yinjiang Tang, and Beibei Yang contributed to the design and data acquisition. Beibei Yang and Dongmei Liu contributed to the data analysis, discussion, and manuscript writing. Dongmei Liu and Changyu Yang contributed to imaging data acquisition and data analysis. Yali Zhou and Guiping Liao contributed to data acquisition. Jian Huang and Yingying Li contributed to scheduling patient follow-ups. All authors reviewed the manuscript.

Data Availability Statement. The data are available from the corresponding author upon reasonable request.

Beibei Yang[1,†], Dongmei Liu[1,†], Changyu Yang[1], Yali zhou[1], Guiping Liao[1], Jian Huang[1], Yingying Li[1], Yinjiang Tang[2] and Xiaolin Yin[1].

[1] Department of Hematology, The 923rd Hospital of the Joint Logistics Support Force of the People's Liberation Army, Nanning, Guangxi, China.
[2] Department of Pulmonary Vascular and General Medicine, Fuwai Yunnan Cardiovascular Hospital, Kunming, Yunnan, China.
[†] These authors have contributed equally to this work.

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Yinjiang Tang, Department of Pulmonary Vascular and General Medicine, Fuwai Yunnan Cardiovascular Hospital, Kunming, Yunnan, CHINA; E-mail: tangyinjiang1@126.com.
Xiaolin Yin, Department of Hematology, The 923rd Hospital of the Joint Logistics Support Force of the People's Liberation Army, Nanning, Guangxi, CHINA; E-mail: yin-xl@163.com

References:

1. Taher AT, Musallam KM, Karimi M, El-Beshlawy A, Belhoul K, Daar S, et al. Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: The optimal care study. Blood 2010;115:1886-92. https://doi.org/10.1182/blood-2009-09-243154 PMid:20032507
2. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, Mcgoon MD. An Evaluation of Long-term Survival From Time of Diagnosis in Pulmonary Arterial Hypertension From the REVEAL Registry n.d. https://doi.org/10.1378/chest.11--1460
3. Derchi G, Galanello R, Bina P, Cappellini MD, Piga A, Lai ME, et al. Prevalence and risk factors for pulmonary arterial hypertension in a large group of β-thalassemia patients using right heart catheterization: A webthal study. Circulation 2014;129:338-45. https://doi.org/10.1161/CIRCULATIONAHA.113.002124 PMid:24081970
4. Ferrari B, Peyvandi F. How I treat thrombotic thrombocytopenic purpura in pregnancy. Blood 2020;136:2125-32. https://doi.org/10.1182/blood.2019000962 PMid:32797178
5. Angelucci E. A new medical therapy for anemia in thalassemia. Blood 2019;133:1267-8. https://doi.org/10.1182/blood-2019-01-897587 PMid:30898772
6. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-731. https://doi.org/10.1093/eurheartj/ehac237 PMid:36017548
7. Fraidenburg DR, Machado RF. Pulmonary hypertension associated with thalassemia syndromes. Ann N Y Acad Sci 2016;1368:127-39. https://doi.org/10.1111/nyas.13037 PMid:27008311 PMCid:PMC4870173
8. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-731. https://doi.org/10.1093/eurheartj/ehac237 PMid:36017548
9. Taher AT, Cappellini MD, Kattamis A, Voskaridou E, Perrotta S, Piga AG, et al. Luspatercept for the treatment of anaemia in non-transfusion-dependent β-thalassaemia (BEYOND): a phase 2, randomised, double-blind, multicentre, placebo-controlled trial. Lancet Haematol 2022;9:e733-44. https://doi.org/10.1016/S2352-3026(22)00208-3
10. Morris CR, Kim HY, Klings ES, Wood J, Porter JB, Trachtenberg F, et al. Dysregulated arginine metabolism and cardiopulmonary dysfunction in patients with thalassaemia. Br J Haematol 2015;169:887-98. https://doi.org/10.1111/bjh.13452 PMid:25907665 PMCid:PMC4452408
11. Platzbecker U, Della Porta MG, Santini V, Zeidan AM, Komrokji RS, Shortt J, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. The Lancet 2023;402:373-85. https://doi.org/10.1016/S0140-6736(23)00874-7 PMid:37311468
12. Sheida Hayati, Amer M. Zeidan, Guillermo Garcia-Manero, Uwe Platzbecker, Aarif Ahsan, Amit K. Verma, Srinivas Aluri, Manuel Ugidos Guerrero, Anita K. Gandhi, Rajasekhar N.V.S. Suragani, Sadanand Vodala. Luspatercept modulates inflammation in the bone marrow, restores effective erythropoiesis/ hematopoiesis, and provides sustained clinical benefit versus epoetin alfa: biomarker analysis from the phase 3 COMMANDS study. Presented at the American Society of Hematology (ASH) Annual Meeting 2023.
13. Maroof Hasan. Luspatercept reduces clonal hematopoiesis-associated cardiac stress via modulation of mTORC1 and inflammatory signaling pathways. Presented at the American Society of Hematology (ASH) Annual Meeting 2024 2024. https://doi.org/10.1182/blood-2024-194241
14. Cappellini MD, Porter J, Origa R, Forni GL, Voskaridou E, Galactéros F, et al. Sotatercept, a novel transforming growth factor β ligand trap, improves anemia in β-thalassemia: A phase II, open-label, dose-finding study. Haematologica 2019;104:477-84. https://doi.org/10.3324/haematol.2018.198887 PMid:30337358 PMCid:PMC6395345
15. Humbert M, McLaughlin V, Gibbs JSR, Gomberg-Maitland M, Hoeper MM, Preston IR, et al. Sotatercept for the Treatment of Pulmonary Arterial Hypertension. New England Journal of Medicine 2021;384:1204-15. https://doi.org/10.1056/NEJMoa2024277 PMid:33789009
16. Hoeper MM, Badesch DB, Ghofrani HA, Gibbs JSR, Gomberg-Maitland M, McLaughlin V V., et al. Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension. New England Journal of Medicine 2023;388:1478-90. https://doi.org/10.1056/NEJMoa2213558 PMid:36877098
17. Brancaleoni V, Nava I, Delbini P, Duca L, Motta I. Activin receptor-ligand trap for the treatment of β-thalassemia: A serendipitous discovery. Mediterr J Hematol Infect Dis 2020;12. https://doi.org/10.4084/mjhid.2020.075 PMid:33194149 PMCid:PMC7643807