

ERİŞKİN TALASEMİ HASTALARINDA TEDAVİ YAKLAŞIMLARI

**21.
BÖLÜM**

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Giriş

Talasemide tedavi yönetimi; anemi yönetimi ve transfüzyon, hastalık komplikasyonlarının izlenmesi ve yönetimi, şelasyon tedavisi, hematopoetik hücre nakli ve gen tedavisinden oluşmaktadır. Tüm tedavi imkânlarında bile hastalık komplikasyonları halen en önemli sorundur. Oral demir şelatörlerinin kullanılmasıyla beraber hastalık komplikasyonlarında azalma görülmekle beraber, hastalığın прогнозunda belirgin iyileşmeler gözlenmiştir. Hematopoetik kök hücre nakli tek kesin tedavi yöntemidir.

Anemi Yönetimi ve Transfüzyon

Anemi ile ilişkili semptomları ve morbiditeleri azaltarak; bozulmuş büyümeye ve gelişme, kemik genişlemesi, hipersplenizm ile ilişkili birtakım morbiditelere yol açabilen ekstramedüller hematopoezin azaltılması veya önlenmesi ve artan bağırsak demir emilimi ve/veya transfüzyonu ile ilişkili aşırı demir depolarının azaltılması amaçlanmıştır (1-8).

Talasemi hastalarındaki en önemli tedavi yaklaşımlarından birisi kan transfüzyon yönetimidir. Düzenli ve yeterli düzeyde kan transfüzyonu ile dokulara yeterli miktarda oksijen taşımaktadır. Talasemide hemoglobini hem anemi semptomlarını azaltan hem de en azından ekstramedüller hematopoezi baskılayan bir seviyede tutmak için kronik transfüzyonlar kullanılır. Bu nedenle, daha yüksek pretransfüzyon hemoglobin değerleri hedeflenir (9 ila 10 veya 9,5 ila 10,5 g / dL) (9).

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Sonuç

Talasemide tedavi yönetimi; anemi ve transfüzyon, talasemi komplikasyonlarının yönetimi, şelasyon tedavisi, hematopoetik hücre nakli ve gen tedavisini içeren, yakın ve düzenli takip gerektiren uzun bir süreçtir.

KAYNAKÇA

1. Rachmilewitz EA, Giardina PJ. How I treat thalassemia. *Blood* 2011; 118:3479.
2. Higgs DR, Engel JD, Stamatoyannopoulos G. Thalassaemia. *Lancet* 2012; 379:373.
3. Liu C, Grossman BJ. Red blood cell transfusion for hematologic disorders. *Hematology Am Soc Hematol Educ Program* 2015; 2015:454.
4. Musallam KM, Rivella S, Vichinsky E, Rachmilewitz EA. Non-transfusion-dependent thalassemias. *Haematologica* 2013; 98:833.
5. Rund D, Rachmilewitz E. Beta-thalassemia. *N Engl J Med* 2005; 353:1135.
6. Taher AT, Musallam KM, Cappellini MD, Weatherall DJ. Optimal management of β thalassaemia intermedia. *Br J Haematol* 2011; 152:512.
7. Borgna-Pignatti C. Modern treatment of thalassaemia intermedia. *Br J Haematol* 2007; 138:291.
8. Olivieri NF. The beta-thalassemias. *N Engl J Med* 1999; 341:99.
9. Cazzola M, Borgna-Pignatti C, Locatelli F, et al. A moderate transfusion regimen may reduce iron loading in beta-thalassemia major without producing excessive expansion of erythropoiesis. *Transfusion* 1997; 37:135.
10. de Alarcon PA, Donovan ME, Forbes GB, et al. Iron absorption in the thalassemia syndromes and its inhibition by tea. *N Engl J Med* 1979; 300:5.
11. Muncie HL Jr, Campbell J. Alpha and beta thalassemia. *Am Fam Physician* 2009; 80:339.
12. Carr S, Rubin L, Dixon D, et al. Intrauterine therapy for homozygous alpha-thalassemia. *Obstet Gynecol* 1995; 85:876.
13. Singer ST, Styles L, Bojanowski J, et al. Changing outcome of homozygous alpha-thalassemia: cautious optimism. *J Pediatr Hematol Oncol* 2000; 22:539.
14. Yi JS, Moertel CL, Baker KS. Homozygous alpha-thalassemia treated with intrauterine transfusions and unrelated donor hematopoietic cell transplantation. *J Pediatr* 2009; 154:766.
15. Lee SY, Chow CB, Li CK, Chiu MC. Outcome of intensive care of homozygous alpha-thalassaemia without prior intra-uterine therapy. *J Paediatr Child Health* 2007; 43:546.
16. Lücke T, Pfister S, Dürken M. Neurodevelopmental outcome and haematological course of a long-time survivor with homozygous alpha-thalassaemia: case report and review of the literature. *Acta Paediatr* 2005; 94:1330.
17. Aessopos A, Kati M, Meletis J. Thalassemia intermedia today: should patients regularly receive transfusions? *Transfusion* 2007; 47:792.
18. Abdelrazik AM, Elshafie SM, El Said MN, et al. Study of red blood cell alloimmunization risk factors in multiply transfused thalassemia patients: role in improving thalassemia transfusion practice in Fayoum, Egypt. *Transfusion* 2016; 56:2303.
19. Datta SS, Mukherjee S, Talukder B, et al. Frequency of Red Cell Alloimmunization and Autoimmunization in Thalassemia Patients: A Report from Eastern India. *Adv*

- Hematol 2015; 2015:610931.
20. Dhawan HK, Kumawat V, Marwaha N, et al. Alloimmunization and autoimmunization in transfusion dependent thalassemia major patients: Study on 319 patients. Asian J Transfus Sci 2014; 8:84.
 21. Chou ST, Liem RI, Thompson AA. Challenges of alloimmunization in patients with haemoglobinopathies. Br J Haematol 2012; 159:394.
 22. Azarkeivan A, Ansari S, Ahmadi MH, et al. Blood transfusion and alloimmunization in patients with thalassemia: multicenter study. Pediatr Hematol Oncol 2011; 28:479.
 23. Vichinsky E, Neumayr L, Trimble S, et al. Transfusion complications in thalassemia patients: a report from the Centers for Disease Control and Prevention (CME). Transfusion 2014; 54:972.
 24. Singer ST, Wu V, Mignacca R, et al. Alloimmunization and erythrocyte autoimmunization in transfusion-dependent thalassemia patients of predominantly asian descent. Blood 2000; 96:3369.
 25. Spanos T, Karageorga M, Ladis V, et al. Red cell alloantibodies in patients with thalassemia. Vox Sang 1990; 58:50.
 26. Michail-Merianou V, Pamphili-Panousopoulou L, Piperi-Lowes L, et al. Alloimmunization to red cell antigens in thalassemia: comparative study of usual versus better-match transfusion programmes. Vox Sang 1987; 52:95.
 27. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761136lbl.pdf (Accessed on November 08, 2019).
 28. Cappellini MD, Viprakasit V, Taher AT, et al. A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia. N Engl J Med 2020; 382:1219.
 29. Piga A, Perrotta S, Gamberini MR, et al. Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with β-thalassemia. Blood 2019; 133:1279.
 30. Suragani RN, Cawley SM, Li R, et al. Modified activin receptor IIB ligand trap mitigates ineffective erythropoiesis and disease complications in murine β-thalassemia. Blood 2014; 123:3864.
 31. Angelucci E. A new medical therapy for anemia in thalassemia. Blood 2019; 133:1267.
 32. Graziano JH, Piomelli S, Hilgartner M, et al. Chelation therapy in beta-thalassemia major. III. The role of splenectomy in achieving iron balance. J Pediatr 1981; 99:695.
 33. Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in beta-thalassemia major. Blood 2008; 111:583.
 34. Cappellini MD, Robbiolo L, Bottasso BM, et al. Venous thromboembolism and hypercoagulability in splenectomized patients with thalassaemia intermedia. Br J Haematol 2000; 111:467.
 35. <http://thalassemia.com/treatment-checklist.aspx#gsc.tab=0> (Accessed on July 21, 2017).
 36. Pennell DJ, Udelson JE, Arai AE, et al. Cardiovascular function and treatment in β-thalassemia major: a consensus statement from the American Heart Association. Circulation 2013; 128:281
 37. Hahalis G, Alexopoulos D, Kremastinos DT, Zoumbos NC. Beta-talassemi sendromunda kalp yetmezliği: on yıllık bir ilerleme. Am J Med 2005; 118: 957.
 38. Aessopos A, Farmakis D, Karagiorga M, vd. Talassemi intermedia'da kardiyak tutu-

- lum: çok merkezli bir çalışma. *Blood* 2001; 97: 3411.
39. Detchaporn P, Kukongviriyapan U, Prawan A, et al. Pediatrik talasemi hastalarında değişen vasküler fonksiyon, arteriyel sertlik ve antioksidan gen yanıtları. *Pediatr Cardiol* 2012; 33: 1054.
 40. Ferrara M, Matarese SM, Francese M, vd. Homozigöz beta talasemi hastalarında sol kalp yetmezliğinde apolipoprotein E (APOE) polimorfizminin rolü. *Br J Haematol* 2001; 114: 959.
 41. Miyata M, Smith JD. Apolipoprotein E alele özgü antioksidan aktivite ve oksidatif haretler ve beta-amiloid peptitler tarafından sitotoksite üzerine etkileri. *Nat Genet* 1996; 14:55.
 42. Talasemi majöründe Origa R, Satta S, Matta G, Galanello R. Glutatyon S-transferaz gen polimorfizmi ve kardiyak demir aşırı yüklenmesi. *Br J Haematol* 2008; 142: 143.
 43. Wood JC, Claster S, Carson S, vd. Talasemi major'da D vitamini eksikliği, kardiyak demir ve kardiyak fonksiyon. *Br J Haematol* 2008; 141: 891.
 44. Detterich J, Noetzli L, Dorey F, et al. Electrocardiographic consequences of cardiac iron overload in thalassemia major. *Am J Hematol* 2012; 87:139.
 45. Hahalis G, Manolis AS, Gerasimidou I, et al. Right ventricular diastolic function in beta-thalassemia major: echocardiographic and clinical correlates. *Am Heart J* 2001; 141:428.
 46. Kostopoulou AG, Tsipras DP, Chaidaroglou AS, et al. The pathophysiological relationship and clinical significance of left atrial function and left ventricular diastolic dysfunction in β-thalassemia major. *Am J Hematol* 2014; 89:13.
 47. Hahalis G, Manolis AS, Apostolopoulos D, et al. Right ventricular cardiomyopathy in beta-thalassaemia major. *Eur Heart J* 2002; 23:147.
 48. Davis BA, O'Sullivan C, Jarritt PH, Porter JB. Value of sequential monitoring of left ventricular ejection fraction in the management of thalassemia major. *Blood* 2004; 104:263.
 49. Wood JC, Enriquez C, Ghugre N, et al. Physiology and pathophysiology of iron myocardopathy in thalassemiamajor. *Ann NY Acad Sci*. 2005; 1054:386-395.
 50. Pennell DJ. T2* magnetic resonance and myocardial iron in thalassemia. *Ann NY Acad Sci*. 2005; 1054:373-378.
 51. Fung EB, Harmatz PR, Lee PD, et al. Increased prevalence of iron-overload associated endocrinopathy in thalassaemia versus sickle-cell disease. *Br J Haematol* 2006; 135:574.
 52. Noetzli LJ, Panigrahy A, Mittelman SD, et al. Pituitary iron and volume predict hypogonadism in transfusional iron overload. *Am J Hematol* 2012; 87:167.
 53. Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Hematologica* 2004; 89:1187.
 54. De Sanctis V, Eleftheriou A, Malaventura C, Thalassaemia International Federation Study Group on Growth and Endocrine Complications in Thalassaemia. Prevalence of endocrine complications and short stature in patients with thalassaemia major: a multicenter study by the Thalassaemia International Federation (TIF). *Pediatr Endocrinol Rev* 2004; 2 Suppl 2:249.
 55. Gamberini MR, Fortini M, De Sanctis V, et al. Diabetes mellitus and impaired glucose tolerance in thalassaemia major: incidence, prevalence, risk factors and survival in patients followed in the Ferrara Center. *Pediatr Endocrinol Rev* 2004; 2 Suppl

- 2:285.
56. Merkel PA, Simonson DC, Amiel SA, et al. Insulin resistance and hyperinsulinemia in patients with thalassemia major treated by hypertransfusion. *N Engl J Med* 1988; 318:809.
 57. Casale M, Citarella S, Filosa A, et al. Endocrine function and bone disease during long-term chelation therapy with deferasirox in patients with β -thalassemia major. *Am J Hematol* 2014; 89:1102.
 58. Naselli A, Vignolo M, Di Battista E, et al. Long-term follow-up of skeletal dysplasia in thalassaemia major. *J Pediatr Endocrinol Metab* 1998; 11 Suppl 3:817.
 59. Noetzli LJ, Mittelman SD, Watanabe RM, et al. Pancreatic iron and glucose dysregulation in thalassemia major. *Am J Hematol* 2012; 87:155.
 60. Pepe A, Meloni A, Rossi G, et al. Cardiac complications and diabetes in thalassaemia major: a large historical multicentre study. *Br J Haematol* 2013; 163:520.
 61. Vogiatzi MG, Macklin EA, Trachtenberg FL, et al. Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassaemia syndromes in North America. *Br J Haematol* 2009; 146:546.
 62. Galanello R, Campus S. Deferiprone chelation therapy for thalassemia major. *Acta Haematol* 2009; 122:155.
 63. Erdoğan E, Canatan D, Ormeci AR, et al. The effects of chelators on zinc levels in patients with thalassemia major. *J Trace Elem Med Biol* 2013; 27:109.
 64. Vatanavicharn S, Pringsulka P, Kritalugsana S, et al. Zinc and copper status in hemoglobin H disease and beta-thalassemia/hemoglobin E disease. *Acta Haematol* 1982; 68:317.
 65. Farmaki K, Tzoumari I, Pappa C, et al. Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major. *Br J Haematol* 2010; 148:466.
 66. Noureldine MHA, Taher AT, Haydar AA, et al. Rheumatological complications of beta-thalassaemia: an overview. *Rheumatology (Oxford)* 2018; 57:19.
 67. Chatterjee R, Shah FT, Davis BA, et al. Prospective study of histomorphometry, biochemical bone markers and bone densitometric response to pamidronate in β -thalassaemia presenting with osteopenia-osteoporosis syndrome. *Br J Haematol* 2012; 159:462.
 68. De Sanctis V, Soliman AT, Elsedfy H, et al. Osteoporosis in thalassemia major: an update and the I-CET 2013 recommendations for surveillance and treatment. *Pediatr Endocrinol Rev* 2013; 11:167.
 69. Haidar R, Mhaidli H, Musallam KM, Taher AT. The spine in β -thalassemia syndromes. *Spine (Phila Pa 1976)* 2012; 37:334.
 70. Vichinsky EP. The morbidity of bone disease in thalassemia. *Ann N Y Acad Sci* 1998; 850:344.
 71. Engkakul P, Mahachoklertwattana P, Jaovisidha S, et al. Unrecognized vertebral fractures in adolescents and young adults with thalassemia syndromes. *J Pediatr Hematol Oncol* 2013; 35:212.
 72. Perrotta S, Cappellini MD, Bertoldo F, et al. Osteoporosis in beta-thalassaemia major patients: analysis of the genetic background. *Br J Haematol* 2000; 111:461.
 73. Dresner Pollack R, Rachmilewitz E, Blumenfeld A, et al. Bone mineral metabolism in adults with beta-thalassaemia major and intermedia. *Br J Haematol* 2000; 111:902.
 74. Ferrara M, Matarese SM, Francese M, et al. Effect of VDR polymorphisms on growth

- and bone mineral density in homozygous beta thalassaemia. *Br J Haematol* 2002; 117:436.
75. Voskaridou E, Kyrtsonis MC, Terpos E, et al. Bone resorption is increased in young adults with thalassaemia major. *Br J Haematol* 2001; 112:36.
 76. Bielinski BK, Darbyshire PJ, Mathers L, et al. Impact of disordered puberty on bone density in beta-thalassaemia major. *Br J Haematol* 2003; 120:353.
 77. Multicentre study on prevalence of endocrine complications in thalassaemia major. Italian Working Group on Endocrine Complications in Non-endocrine Diseases. *Clin Endocrinol (Oxf)* 1995; 42:581.
 78. Voskaridou E, Terpos E. New insights into the pathophysiology and management of osteoporosis in patients with beta thalassaemia. *Br J Haematol* 2004; 127:127.
 79. Tsay J, Yang Z, Ross FP, et al. Bone loss caused by iron overload in a murine model: importance of oxidative stress. *Blood* 2010; 116:2582.
 80. Rossi F, Perrotta S, Bellini G, et al. Iron overload causes osteoporosis in thalassemia major patients through interaction with transient receptor potential vanilloid type 1 (TRPV1) channels. *Haematologica* 2014; 99:1876.
 81. Chan YL, Li CK, Pang LM, Chik KW. Desferrioxamine-induced long bone changes in thalassaemic patients - radiographic features, prevalence and relations with growth. *Clin Radiol* 2000; 55:610.
 82. Naselli A, Vignolo M, Di Battista E, et al. Long-term follow-up of skeletal dysplasia in thalassaemia major. *J Pediatr Endocrinol Metab* 1998; 11 Suppl 3:817.
 83. Fung EB, Kwiatkowski JL, Huang JN, et al. Zinc supplementation improves bone density in patients with thalassemia: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr* 2013; 98:960.
 84. Bekheirnia MR, Shamshirsaz AA, Kamgar M, et al. Serum zinc and its relation to bone mineral density in beta-thalassemic adolescents. *Biol Trace Elem Res* 2004; 97:215.
 85. Mutlu M, Argun M, Kilic E, et al. Magnesium, zinc and copper status in osteoporotic, osteopenic and normal post-menopausal women. *J Int Med Res* 2007; 35:692.
 86. Voskaridou E, Terpos E, Spina G, et al. Pamidronate is an effective treatment for osteoporosis in patients with beta-thalassaemia. *Br J Haematol* 2003; 123:730.
 87. Otrack ZK, Azar ST, Shamseddeen WA, et al. Intravenous zoledronic acid treatment in thalassemia-induced osteoporosis: results of a phase II clinical trial. *Ann Hematol* 2006; 85:605.
 88. Mamtani M, Kulkarni H. Bone recovery after zoledronate therapy in thalassemia-induced osteoporosis: a meta-analysis and systematic review. *Osteoporos Int* 2010; 21:183.
 89. Taher AT, Musallam KM, Karimi M, 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.
 90. Matta BN, Abbas O, Maakaron JE, et al. Leg ulcers in patients with β -thalassae-mia intermedia: a single centre's experience. *J Eur Acad Dermatol Venereol* 2014; 28:1245.
 91. Musallam KM, Taher AT, Rachmilewitz EA. β -thalassemia intermedia: a clinical perspective. *Cold Spring Harb Perspect Med* 2012; 2:a013482.
 92. Aessopos A, Kati M, Tsironi M, et al. Exchange blood transfusions for the treatment of leg ulcerations in thalassemia intermedia. *Haematologica* 2006; 91:ECR11.

93. Gamberini MR, Fortini M, De Sanctis V. Healing of leg ulcers with hydroxyurea in thalassaemia intermedia patients with associated endocrine complications. *Pediatr Endocrinol Rev* 2004; 2 Suppl 2:319.
94. Aydinok Y, Bayraktaroglu S, Yildiz D, Alper H. Myocardial iron loading in patients with thalassemia major in Turkey and the potential role of splenectomy in myocardial siderosis. *J Pediatr Hematol Oncol* 2011;33:374-378.
95. Aydinok Y, Kattamis A, Viprakasit V. Current approach to iron chelation in children. *Br J Haematol* 2014; 165:745.
96. Olivier NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. *Blood* 1997; 89:739.
97. Hoffbrand AV, Taher A, Cappellini MD. How I treat transfusional iron overload. *Blood* 2012; 120:3657.
98. Pennell DJ, Berdoukas V, Karagiorga M, et al. Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. *Blood* 2006; 107:3738.
99. Maggio A, Vitrano A, Capra M, et al. Improving survival with deferiprone treatment in patients with thalassemia major: a prospective multicenter randomised clinical trial under the auspices of the Italian Society for Thalassemia and Hemoglobinopathies. *Blood Cells Mol Dis* 2009; 42:247.
100. Lai ME, Grady RW, Vacquer S, et al. Increased survival and reversion of iron-induced cardiac disease in patients with thalassemia major receiving intensive combined chelation therapy as compared to desferoxamine alone. *Blood Cells Mol Dis* 2010; 45:136.
101. Davis BA, O'Sullivan C, Jarritt PH, Porter JB. Value of sequential monitoring of left ventricular ejection fraction in the management of thalassemia major. *Blood* 2004; 104:263.
102. Anderson LJ, Westwood MA, Holden S, et al. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. *Br J Haematol* 2004; 127:348.
103. Boelaert JR, de Locht M, Van Cutsem J, et al. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies. *J Clin Invest* 1993; 91:1979.
104. Green NS. Yersinia infections in patients with homozygous beta-thalassemia associated with iron overload and its treatment. *Pediatr Hematol Oncol* 1992; 9:247.
105. Bunce PE, Mishra S, Gold WL. Iron-clad diagnosis. *Am J Med* 2008; 121:1043.
106. Tanner MA, Galanello R, Dessi C, et al. A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. *Circulation* 2007; 115:1876.
107. Anderson LJ, Wonke B, Prescott E, et al. Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia. *Lancet* 2002; 360:516.
108. Borgna-Pignatti C, Cappellini MD, De Stefano P, et al. Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia major. *Blood* 2006; 107:3733.
109. Pepe A, Rossi G, Meloni A, et al. A T2* MRI prospective survey on heart and liver

- iron in thalassemia major patients treated with deferasirox versus deferiprone and desferrioxamine in monotherapy. (Abstract 4267). *Blood* 2010; 116:1731.
110. Taher AT, Porter JB, Viprakasit V, et al. Deferasirox demonstrates a dose-dependent reduction in liver iron concentration and consistent efficacy across subgroups of non-transfusion-dependent thalassemia patients. *Am J Hematol* 2013; 88:503.
111. Galanello R. Deferiprone in the treatment of transfusion-dependent thalassemia: a review and perspective. *Ther Clin Risk Manag* 2007; 3:795.
112. Pennell DJ, Porter JB, Cappellini MD, et al. Deferasirox for up to 3 years leads to continued improvement of myocardial T2* in patients with β -thalassemia major. *Haematologica* 2012;97:842-848.
113. Wonke B, Wright C, Hoffbrand AV. Combined therapy with deferiprone and desferrioxamine. *Br J Haematol* 1998; 103:361.
114. Maggio A, Vitrano A, Capra M, et al. Long-term sequential deferiprone-desferrioxamine versus deferiprone alone for thalassaemia major patients: a randomized clinical trial. *Br J Haematol* 2009; 145:245.
115. Fabio G, Minonzio F, Delbini P, et al. Reversal of cardiac complications by deferiprone and deferoxamine combination therapy in a patient affected by a severe type of juvenile hemochromatosis (JH). *Blood* 2007; 109:362.
116. Tanner MA, Galanello R, Densi C, et al. Combined chelation therapy in thalassemia major for the treatment of severe myocardial siderosis with left ventricular dysfunction. *J Cardiovasc Magn Reson* 2008; 10:12.
117. Lucarelli G, Galimberti M, Polchi P, et al. Bone marrow transplantation in patients with thalassemia. *N Engl J Med* 1990; 322:417.
118. Angelucci E. Hematopoietic stem cell transplantation in thalassemia. *Hematology Am Soc Hematol Educ Program* 2010; 2010:456.
119. Lucarelli G, Galimberti M, Polchi P, et al. Marrow transplantation in patients with thalassemia responsive to iron chelation therapy. *N Engl J Med* 1993; 329:840.
120. Lucarelli G, Clift RA, Galimberti M, et al. Marrow transplantation for patients with thalassemia: results in class 3 patients. *Blood* 1996; 87:2082.
121. Lucarelli G, Clift RA, Galimberti M, et al. Bone marrow transplantation in adult thalassemic patients. *Blood* 1999; 93:1164.
122. Baronciani D, Angelucci E, Potschger U, et al. Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000-2010. *Bone Marrow Transplant* 2016; 51:536.
123. Cohen AR, Martin M, Schwartz E. Current treatment of Cooley's anemia. Intravenous chelation therapy. *Ann N Y Acad Sci* 1990;612:286-292.
124. Srivastava A, Shaji RV. Cure for thalassemia major - from allogeneic hematopoietic stem cell transplantation to gene therapy. *Haematologica* 2017; 102:214.
125. Thompson AA, Walters MC, Kwiatkowski J, et al. Gene Therapy in Patients with Transfusion-Dependent β -Thalassemia. *N Engl J Med* 2018; 378:1479.
126. Marktel S, Scaramuzza S, Cicalese MP, et al. Intrabone hematopoietic stem cell gene therapy for adult and pediatric patients affected by transfusion-dependent β -thalassemia. *Nat Med* 2019; 25:234.
127. Miccio A, Cesari R, Lotti F, et al. In vivo selection of genetically modified erythroid progenitors leads to long-term correction of beta-thalassemia. *Proc Natl Acad Sci U S A* 2008; 105:10547.

128. May C, Rivella S, Chadburn A, Sadelain M. Successful treatment of murine beta-thalassemia intermedia by transfer of the human beta-globin gene. *Blood* 2002; 99:1902.
129. Rivella S, May C, Chadburn A, et al. A novel murine model of Cooley anemia and its rescue by lentiviral-mediated human beta-globin gene transfer. *Blood* 2003; 101:2932.
130. Persons DA, Allay ER, Sawai N, et al. Successful treatment of murine beta-thalassemia using in vivo selection of genetically modified, drug-resistant hematopoietic stem cells. *Blood* 2003; 102:506.
131. Huo Y, McConnell SC, Ryan TM. Preclinical transfusion-dependent humanized mouse model of beta thalassemia major. *Blood* 2009; 113:4763.
132. Cavazzana-Calvo M, Payen E, Negre O, et al. Transfusion independence and HMGA2 activation after gene therapy of human β-thalassaemia. *Nature* 2010; 467:318.
133. Baum C, Düllmann J, Li Z, et al. Side effects of retroviral gene transfer into hematopoietic stem cells. *Blood* 2003; 101:2099.
134. Quek L, Thein SL. Molecular therapies in beta-thalassaemia. *Br J Haematol* 2007; 136:353.
135. Nienhuis AW. Development of gene therapy for blood disorders. *Blood* 2008; 111:4431.
136. Atweh GF, Forget BG. Clinical applications of gene therapy: anemias. In: *Stem Cell Biology and Gene Therapy*, esenberry PJ, Stein GS, Forget BG (Eds), John Wiley, New York 1998. p.411.
137. Nicolini FE, Imren S, Oh IH, et al. Expression of a human beta-globin transgene in erythroid cells derived from retrovirally transduced transplantable human fetal liver and cord blood cells. *Blood* 2002; 100:1257.
138. Puthenveetil G, Scholes J, Carbonell D, et al. Successful correction of the human beta-thalassemia major phenotype using a lentiviral vector. *Blood* 2004; 104:3445.
139. May C, Rivella S, Callegari J, et al. Therapeutic haemoglobin synthesis in beta-thalassaemic mice expressing lentivirus-encoded human beta-globin. *Nature* 2000; 406:82.
140. Persons DA, Allay ER, Sabatino DE, et al. Functional requirements for phenotypic correction of murine beta-thalassemia: implications for human gene therapy. *Blood* 2001; 97:3275.
141. Wilber A, Hargrove PW, Kim YS, et al. Therapeutic levels of fetal hemoglobin in erythroid progeny of β-thalassemic CD34+ cells after lentiviral vector-mediated gene transfer. *Blood* 2011; 117:2817.
142. Liu Y, Yang Y, Kang X, et al. One-Step Biallelic and Scarless Correction of a β-Thalassemia Mutation in Patient-Specific iPSCs without Drug Selection. *Mol Ther Nucleic Acids* 2017; 6:57.