# BÖLÜM 2
# Trombopoetin: Biyolojisi ve Potansiyel Klinik Alandaki Durum ve Uygulamaları

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## Biyolojisi

Trombopoetin (TPO) megakaryosit ve trombosit yapımını MPL reseptörü (TPO-R) üzerinden regüle eden glikoprotein yapısında bir sitokindir. MPL reseptörü 1992'de (1) TPO 1994'de tanımlanmıştır (2, 3). TPO ana olarak karaciğerde, daha az olarak kemik iliği ve böbrek parankim hücrelerinde 353 aminoasit olarak sentez edilir (4). 153 aminoasitlik eritropoetin ile benzer domain (TPO153) ihtiva eder (5). TPO reseptörleri trombositler, megakaryositler, CD34+ öncül hücrelerde bulunur (6). Megakaryositlerin sayısında artışı, apoptozunun azalmasını ve matürasyonununu sağlar (7). TPO selüler etkisi JAK, STAT ve MAP kinaz üzerinden olur. TPO etkisi ile ilk 4 gün kemik iliğindeki megakaryosit sayısı artar fakat dolaşımdaki trombosit sayısı değişmez. Beşinci gün trombosit sayısında artış olmaya başlar, TPO verilmeye devam edilirse 8-12. günde trombosit sayısı platoya ulaşır. TPO uygulaması kesildikten sonra trombosit sayıları 10 günde normale döner (8, 9).

Hepatik TPO sentezi, özel bir düzenlemeye tabii değildir ve daha çok üretilen TPO'nun klirensi üzerinden regüle edilir (10). TPO klirensi trombositler üzerindeki c-mpl reseptörüne bağlanması ile olmaktadır. Trombosit sayısı arttığında TPO düzeyi düşer (11). TPO düzeyleri aplastik anemide belirgin artarken immun trombositopenide (ITP) daha az artmıştır (12, 13). TPO ana olarak karaciğerde üretildiği için karaciğer yetersizliklerinde düzeyi düşer. Bu hastalarda trombositopeni, hipersplenizm ve TPO azalmasına bağlı görülür (14).

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## Kaynaklar


1. Vigon I, Mornon JP, Cocault L, Mitjavila MT, Tambourin P, Gisselbrecht S, et al. Molecular cloning and characterization of MPL, the human homolog of the v-mpl oncogene: identification of a member of the hematopoietic growth factor receptor superfamily. Proceedings of the National Academy of Sciences. 1992;89(12):5640-4.
2. Kato T, Ogami K, Shimada Y, Iwamatsu A, Sohma Y, Akahori H, et al. Purification and characterization of thrombopoietin. J Biochem. 1995;118(1):229-36.
3. Lok S, Kaushansky K, Holly RD, Kuijper JL, Lofton-Day CE, Oort PJ, et al. Cloning and expression of murine thrombopoietin cDNA and stimulation of platelet production in vivo. Nature. 1994;369(6481):565-8.
4. Foster DC, Sprecher CA, Grant FJ, Kramer JM, Kuijper JL, Holly RD, et al. Human thrombopoietin: gene structure, cDNA sequence, expression, and chromosomal localization. Proceedings of the National Academy of Sciences. 1994;91(26):13023-7.
5. Gurney AL, Kuang W-J, Xie M-H, Malloy BE, Eaton DL, de Sauvage FJ. Genomic Structure, Chromosomal Localization, and Conserved Alternative Splice Forms of Thrombopoietin. Blood. 1995;85(4):981-8.
6. Solar GP, Kerr WG, Zeigler FC, Hess D, Donahue C, de Sauvage FJ, et al. Role of c-mpl in Early Hematopoiesis. Blood. 1998;92(1):4-10.
7. Zauli G, Vitale M, Falcieri E, Gibellini D, Bassini A, Celeghini C, et al. In Vitro Senescence and Apoptotic Cell Death of Human Megakaryocytes. Blood. 1997;90(6):2234-43.
8. Kuter DJ, Goodnough LT, Romo J, DiPersio J, Peterson R, Tomita D, et al. Thrombopoietin therapy increases platelet yields in healthy platelet donors. Blood. 2001;98(5):1339-45.
9. Tomita D, Petrarca M, Paine T, Olson K, Roskos L, Cheung E, et al., editors. Effect of a single dose of pegylated human recombinant megakaryocyte growth and development factor (PEG-rHuMGDF) on platelet counts: implications for platelet apheresis. Transfusion; 1997: AMER ASSOC BLOOD BANKS 8101 GLENBROOK RD, BETHESDA, MD 20814-2749.
10. Kuter DJ. Thrombopoietin: biology, clinical applications, role in the donor setting. J Clin Apher. 1996;11(3):149-59.
11. Li J, Xia Y, Kuter DJ. Interaction of thrombopoietin with the platelet c-mpl receptor in plasma: binding, internalization, stability and pharmacokinetics. British journal of haematology. 1999;106(2):345-56.
12. Gu J, Lu L, Xu R, Chen X. Plasma thrombopoietin levels in patients with aplastic anemia and idiopathic thrombocytopenic purpura. Chinese medical journal. 2002;115(7):983-6.
13. Ichikawa N, Ishida F, Shimodaira S, Tahara T, Kato T, Kitano K. Regulation of serum thrombopoietin levels by platelets and megakaryocytes in patients with aplastic anaemia and idiopathic thrombocytopenic purpura. Thrombosis and haemostasis. 1996;76(2):156-60.
14. Giannini EG, Peck-Radosavljevic M. Platelet Dysfunction: Status of Thrombopoietin in Thrombocytopenia Associated with Chronic Liver Failure. Seminars in thrombosis and hemostasis. 2015;41(5):455-61.
15. Li J, Yang C, Xia Y, Bertino A, Glaspy J, Roberts M, et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood. 2001;98(12):3241-8.
16. Nomoto M, Pastino G, Rege B, Aluri J, Ferry J, Han D. Pharmacokinetics, Pharmacodynamics, Pharmacogenomics, Safety, and Tolerability of Avatrombopag in Healthy Japanese and White Subjects. Clin Pharmacol Drug Dev. 2018;7(2):188-95.
17. Terrault N, Chen YC, Izumi N, Kayali Z, Mitrut P, Tak WY, et al. Avatrombopag Before Procedures Reduces Need for Platelet Transfusion in Patients With Chronic Liver Disease and Thrombocytopenia. Gastroenterology. 2018;155(3):705-18.
18. Peck-Radosavljevic M, Simon K, Iacobellis A, Hassanein T, Kayali Z, Tran A, et al. Lusutrombopag for the Treatment of Thrombocytopenia in Patients With Chronic Liver Disease

Undergoing Invasive Procedures (L-PLUS 2). Hepatology. 2019;70(4):1336-48.
19. Psaila B, Bussel JB, Linden MD, Babula B, Li Y, Barnard MR, et al. In vivo effects of eltrombopag on platelet function in immune thrombocytopenia: no evidence of platelet activation. Blood. 2012;119(17):4066-72.
20. Vlachodimitropoulou E, Chen Y-L, Garbowski M, Koonyosying P, Psaila B, Sola-Visner M, et al. Eltrombopag: a powerful chelator of cellular or extracellular iron(III) alone or combined with a second chelator. Blood. 2017;130(17):1923-33.
21. Rodeghiero F, Stasi R, Giagounidis A, Viallard JF, Godeau B, Pabinger I, et al. Long-term safety and tolerability of romiplostim in patients with primary immune thrombocytopenia: a pooled analysis of 13 clinical trials. European journal of haematology. 2013;91(5):423-36.
22. Kuter DJ, Mufti GJ, Bain BJ, Hasserjian RP, Davis W, Rutstein M. Evaluation of bone marrow reticulin formation in chronic immune thrombocytopenia patients treated with romiplostim. Blood. 2009;114(18):3748-56.
23. Brynes RK, Wong RS, Thein MM, Bakshi KK, Burgess P, Theodore D, et al. A 2-Year, Longitudinal, Prospective Study of the Effects of Eltrombopag on Bone Marrow in Patients with Chronic Immune Thrombocytopenia. Acta haematologica. 2017;137(2):66-72.
24. Ghanima W, Geyer JT, Lee CS, Boiocchi L, Imahiyerobo AA, Orazi A, et al. Bone marrow fibrosis in 66 patients with immune thrombocytopenia treated with thrombopoietin-receptor agonists: a single-center, long-term follow-up. Haematologica. 2014;99(5):937-44.
25. Waleed G, Nichola C, Francesco R, Bertrand G, James BB. Thrombopoietin receptor agonists: ten years later. Haematologica. 2019;104(6):1112-23.
26. Kuter DJ, Bussel JB, Newland A, de Wolf JT, Guthrie T, Wasser J, et al. Long-Term Treatment with Romiplostim in Patients with Chronic Immune Thrombocytopenic Purpura (ITP): 3-Year Update from An Open-Label Extension Study. Blood. 2008;112(11):402-.
27. Saleh MN, Bussel JB, Cheng G, Meyer O, Bailey CK, Arning M, et al. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. Blood. 2013;121(3):537-45.
28. Taylor N, Melchardt T, Grundbichler M, Strasser M, Egle A, Greil R. Use of romiplostim allows for hepatitis C therapy in a HIV/HCV coinfected patient. Annals of hematology. 2013;92(7):1001-2.
29. Kuter DJ. What is the role of novel thrombopoietic agents in the management of acute leukemia? Best Practice & Research Clinical Haematology. 2016;29(4):372-8.
30. McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, Bourliere M, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. The New England journal of medicine. 2007;357(22):2227-36.
31. Peck-Radosavljevic M, Wichlas M, Zacherl J, Stiegler G, Stohlawetz P, Fuchsjäger M, et al. Thrombopoietin induces rapid resolution of thrombocytopenia after orthotopic liver transplantation through increased platelet production. Blood. 2000;95(3):795-801.
32. Afdhal NH, Giannini EG, Tayyab G, Mohsin A, Lee JW, Andriulli A, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. The New England journal of medicine. 2012;367(8):716-24.
33. Poordad F, Terrault NA, Alkhouri N, Tian W, Allen LF, Rabinovitz M. Avatrombopag, an Alternate Treatment Option to Reduce Platelet Transfusions in Patients with Thrombocytopenia and Chronic Liver Disease-Integrated Analyses of 2 Phase 3 Studies. Int J Hepatol. 2020;2020:5421632.
34. Sekeres MA, Kantarjian H, Fenaux P, Becker P, Boruchov A, Guerci-Bresler A, et al. Subcutaneous or intravenous administration of romiplostim in thrombocytopenic patients with lower risk myelodysplastic syndromes. Cancer. 2011;117(5):992-1000.
35. Kantarjian H, Fenaux P, Sekeres MA, Becker PS, Boruchov A, Bowen D, et al. Safety and efficacy of romiplostim in patients with lower-risk myelodysplastic syndrome and thrombo-

cytopenia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(3):437-44.
36. Kantarjian HM, Giles FJ, Greenberg PL, Paquette RL, Wang ES, Gabrilove JL, et al. Phase 2 study of romiplostim in patients with low- or intermediate-risk myelodysplastic syndrome receiving azacitidine therapy. Blood. 2010;116(17):3163-70.
37. Mittelman M, Platzbecker U, Afanasyev B, Grosicki S, Wong RSM, Anagnostopoulos A, et al. Eltrombopag for advanced myelodysplastic syndromes or acute myeloid leukaemia and severe thrombocytopenia (ASPIRE): a randomised, placebo-controlled, phase 2 trial. Lancet Haematol. 2018;5(1):e34-e43.
38. Platzbecker U, Wong RS, Verma A, Abboud C, Araujo S, Chiou TJ, et al. Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukaemia: a multicentre, randomised, placebo-controlled, double-blind, phase 1/2 trial. Lancet Haematol. 2015;2(10):e417-26.
39. Kellum A, Jagiello-Gruszfeld A, Bondarenko IN, Patwardhan R, Messam C, Mostafa Kamel Y. A randomized, double-blind, placebo-controlled, dose ranging study to assess the efficacy and safety of eltrombopag in patients receiving carboplatin/paclitaxel for advanced solid tumors. Curr Med Res Opin. 2010;26(10):2339-46.
40. Winer ES, Safran H, Karaszewska B, Richards DA, Hartner L, Forget F, et al. Eltrombopag with gemcitabine-based chemotherapy in patients with advanced solid tumors: a randomized phase I study. Cancer Med. 2015;4(1):16-26.
41. Winer ES, Safran H, Karaszewska B, Bauer S, Khan D, Doerfel S, et al. Eltrombopag for thrombocytopenia in patients with advanced solid tumors receiving gemcitabine-based chemotherapy: a randomized, placebo-controlled phase 2 study. International journal of hematology. 2017;106(6):765-76.
42. Zeigler FC, de Sauvage F, Widmer HR, Keller GA, Donahue C, Schreiber RD, et al. In vitro megakaryocytopoietic and thrombopoietic activity of c-mpl ligand (TPO) on purified murine hematopoietic stem cells. Blood. 1994;84(12):4045-52.
43. Olnes MJ, Scheinberg P, Calvo KR, Desmond R, Tang Y, Dumitriu B, et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. The New England journal of medicine. 2012;367(1):11-9.
44. Vadhan-Raj S, Kavanagh JJ, Freedman RS, Folloder J, Currie LM, Bueso-Ramos C, et al. Safety and efficacy of transfusions of autologous cryopreserved platelets derived from recombinant human thrombopoietin to support chemotherapy-associated severe thrombocytopenia: a randomised cross-over study. Lancet. 2002;359(9324):2145-52.
45. Mahat U, Rotz SJ, Hanna R. Use of Thrombopoietin Receptor Agonists in Prolonged Thrombocytopenia after Hematopoietic Stem Cell Transplantation. Biology of Blood and Marrow Transplantation. 2020;26(3):e65-e73.
46. Basser RL, Rasko JE, Clarke K, Cebon J, Green MD, Grigg AP, et al. Randomized, blinded, placebo-controlled phase I trial of pegylated recombinant human megakaryocyte growth and development factor with filgrastim after dose-intensive chemotherapy in patients with advanced cancer. Blood. 1997;89(9):3118-28.
47. Somlo G, Sniecinski I, ter Veer A, Longmate J, Knutson G, Vuk-Pavlovic S, et al. Recombinant Human Thrombopoietin in Combination With Granulocyte Colony-Stimulating Factor Enhances Mobilization of Peripheral Blood Progenitor Cells, Increases Peripheral Blood Platelet Concentration, and Accelerates Hematopoietic Recovery Following High-Dose Chemotherapy. Blood. 1999;93(9):2798-806.