BÖLÜM 27

P2Y12 İNHİBİTÖRLERİ

Yücel KANAL[1]

GİRİŞ

P2Y12 reseptörleri trombositlerin yüzeylerinde bulunur. Bu reseptörlerin, trombosit aktivasyonu ve agregasyonundaki etkin rolü nedeniyle, inhibisyonları etkin antitrombotik etki yaratmaktadır. Trombosit aktivasyonu gerçekleşirken trombositlerden adenozin difosfat (ADP) salgılanır ve hücre dışında yer alan P2Y12 reseptörleriyle etkileşirler. P2Y12 aktivasyonu trombositin şekil değiştirmesini sağlayıp Gp2b/3a aktivasyonunu sağlarken, aynı zamanda Gp 2b/3a reseptörünün aktivasyonunun sürdürülmesinde de rol alır. Bu durum trombosit agregasyonunun devamlılığı için çok önemlidir.[1] P2Y12 inhibisyonu trombüs agregasyonunu engellediği gibi, agrege olan trombüsün yıkımını da hızlandırır. ADP nin bir diğer etkisi de damar içindeki doku faktörünü inhibe etmesidir. Bu sayede koagülasyonu da etkileyebilir.[1] Tiklopidin, klopidogrel, prasugrel, tikagrelor ve kangrelor molekülleri P2Y12 reseptörünü inhibe eden moleküllerdir. Kangrelor ıntravenöz kullanılırken; tiklopidin, tikagrelor, prasugrel ve klopidogrel oral yolla kullanılmaktadır.

Bu ilaçlar ADP'nin trombositlerdeki P2Y12 reseptörüne bağlanmasını engeller ve böylece trombositlerin fibrinojene ve birbirine bağlanması için gerekli olan Gp 2b/3a reseptörlerinin aktivasyonunu engeller**.** Kangrelor ve tikagrelor P2Y12 ADP reseptörüne reversible bağlanırken; klopidogrel ve prasugrel irreversible olarak bağlanmaktadır (Resim 1). Trombosit agregasyonun maksimum inhibisyonu kangrelor ile 2 dk, tikagrelor ile 1-3 saatte, prasugrel ile 2-4 saatte, tiklopidin ile 3-4 günde, klopidogrel ile 3-5 günde olmaktadır.

[1] Uzm. Dr., Tokat Devlet Hastanesi, Kardiyoloji Bölümü, yucel_kanal@hotmail.com

p=0,005). Sonuç olarak, stent sonrası bir ay DAPT, 12 ay DAPT'a göre daha iyi saptanmıştır.[44] MASTER DAPT (The Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen) çalışmasında bir ay süreli DAPT değerlendirilmiştir. Çalışmaya akut ya da stabil KAH nedeniyle eriyen polimerli DES (Ultimaster, Terumo) takılan, stent takıldıktan sonraki bir ayda majör advers kardiyak olay yaşamayan, kanama riski yüksek hastalar alınmıştır. Hastalar bir ayın sonunda DAPT kesildiği (n=2295) veya en az iki ay daha devam edildiği 2 gruba (n=2284) randomize edilmiştir. Çalışmada 3 primer sonlanım vardır. Bunlar, mutlak klinik olaylar (ölüm, Mİ, inme veya majör kanama toplamı), majör kardiyak veya serebral olaylar (ölüm, Mİ veya inme toplamı), majör veya klinik olarak önemli majör olmayan kanama toplamıdır. İlk iki sonlanım per-protocol non-inferiority, sonuncusu intention to treat superiority şeklinde değerlendirilmiştir. Hastaların %48,3'üne AKS ile stent takılmıştır. 1 ay sonra DAPT durdurulan grupta hastaların %53,9'unda monoterapiye klopidogrelle devam edilmiştir. DAPT'a devam eden hastaların %78,7'sinde klopidogrel kullanmıştır. Mutlak klinik olaylar 1 ay grubunda %7,5 görülürken; devam edilen grupta %7,7 izlenmiştir. (HR 0.97, %95 GA 0.78-1.20, non-inferiority p<0.001). Majör kardiyak ve serebrovasküler olaylar sırasıyla %6,1 ve %5,9'dur (HR 1.02, 0.80-1.30, non-inferiority p=0.001). Majör veya minör kanama sırasıyla %6,5 ve %9,4'tür (HR 0,68, 0,55-0,84, p<0,001). Mİ ve stent trombozu da iki grupta benzerdir. Tüm nedenlere bağlı ölüm iki grupta benzerdir (sırasıyla %3,3 ve %3,6). Bu çalışmanın sonunda 1 aylık DAPT tedavisi ile iskemik olaylarda artış olmaksızın, kanama komplikasyonunda azalma saptanmıştır.[45]

KAYNAKLAR

1. Maree AO, Fitzgerald DJ. Variable platelet response to aspirin and clopidogrel in atherothrombotic disease. Circulation. 2007;115(16):2196-207.
2. Janzon L. The STIMS trial: the ticlopidine experience and its clinical applications. Swedish Ticlopidine Multicenter Study. Vasc Med. 1996;1(2):141-3.
3. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. Am J Med. 2006;119(8):624-38.
4. Bhatt DL, Bertrand ME, Berger PB, L'Allier PL, Moussa I, Moses JW, et al. Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. J Am Coll Cardiol. 2002;39(1):9-14.
5. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57.
6. Task Force for D, Treatment of Non STSEACSoESoC, Bassand JP, Hamm CW, Ardissino D, Boersma E, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2007;28(13):1598-660.
7. Muller I, Seyfarth M, Rudiger S, Wolf B, Pogatsa-Murray G, Schomig A, et al. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. Heart. 2001;85(1):92-3.
8. Antithrombotic Trialists C. Collaborative meta-analysis of randomised trials of antiplatelet

therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329):71-86.
9. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA. 2010;304(16):1821-30.
10. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet. 2010;376(9749):1320-8.
11. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation. 2009;119(19):2553-60.
12. Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Muller U, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. J Am Coll Cardiol. 2012;59(24):2159-64.
13. Hochholzer W, Trenk D, Fromm MF, Valina CM, Stratz C, Bestehorn HP, et al. Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. J Am Coll Cardiol. 2010;55(22):2427-34.
14. Agewall S, Cattaneo M, Collet JP, Andreotti F, Lip GY, Verheugt FW, et al. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. Eur Heart J. 2013;34(23):1708-13, 13a-13b.
15. Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol. 2008;51(3):256-60.
16. Norgard NB, Mathews KD, Wall GC. Drug-drug interaction between clopidogrel and the proton pump inhibitors. Ann Pharmacother. 2009;43(7):1266-74.
17. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39(3):213-60.
18. Dippel DW. The results of CAPRIE, IST and CAST. Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events. International Stroke Trial. Chinese Acute Stroke Trial. Thromb Res. 1998;92(1 Suppl 1):S13-6.
19. Squizzato A, Keller T, Romualdi E, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. Cochrane Database Syst Rev. 2011(1):CD005158.
20. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators C. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation. 2000;102(6):624-9.
21. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358(9281):527-33.
22. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494-502.
23. Aronow HD, Steinhubl SR, Brennan DM, Berger PB, Topol EJ, Investigators C. Bleeding risk associated with 1 year of dual antiplatelet therapy after percutaneous coronary intervention: Insights

from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Am Heart J. 2009;157(2):369-74.
24. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention: results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. Circulation. 2005;111(16):2099-106.
25. Ferguson JJ. Clopidogrel plus aspirin in patients with acute myocardial infarction treated with fibrinolytic therapy--CLARITY-TIMI 28. Future Cardiol. 2005;1(5):605-10.
26. Second Chinese Cardiac Study Collaborative G. Rationale, design and organization of the Second Chinese Cardiac Study (CCS-2): a randomized trial of clopidogrel plus aspirin, and of metoprolol, among patients with suspected acute myocardial infarction. Second Chinese Cardiac Study (CCS-2) Collaborative Group. J Cardiovasc Risk. 2000;7(6):435-41.
27. Wiviott SD, Antman EM, Winters KJ, Weerakkody G, Murphy SA, Behounek BD, et al. Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 antagonist, with clopidogrel in percutaneous coronary intervention: results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial. Circulation. 2005;111(25):3366-73.
28. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001-15.
29. Schupke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wohrle J, et al. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2019;381(16):1524-34.
30. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(23):2999-3054.
31. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372(19):1791-800.
32. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, et al. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. N Engl J Med. 2017;376(1):32-40.
33. Berwanger O, Lopes RD, Moia DDF, Fonseca FA, Jiang L, Goodman SG, et al. Ticagrelor Versus Clopidogrel in Patients With STEMI Treated With Fibrinolysis: TREAT Trial. J Am Coll Cardiol. 2019;73(22):2819-28.
34. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, et al. Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med. 2013;368(14):1303-13.
35. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):1289-367.
36. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J. 2017;38(41):3070-8.
37. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet. 2017;390(10104):1747-57.
38. Kim CJ, Park MW, Kim MC, Choo EH, Hwang BH, Lee KY, et al. Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. Lancet. 2021;398(10308):1305-16.
39. Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, et al. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (fantastic) study. Circulation. 1998;98(16):1597-603.

40. Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH, et al. Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction. J Am Coll Cardiol. 2015;65(20):2211-21.
41. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, et al. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA. 2013;310(23):2510-22.
42. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. Lancet. 2015;385(9985):2371-82.
43. Palmerini T, Bruno AG, Redfors B, Valgimigli M, Taglieri N, Feres F, et al. Risk-Benefit of 1-Year DAPT After DES Implantation in Patients Stratified by Bleeding and Ischemic Risk. J Am Coll Cardiol. 2021;78(20):1968-86.
44. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. JAMA. 2019;321(24):2414-27.
45. Valgimigli M, Frigoli E, Heg D, Tijssen J, Juni P, Vranckx P, et al. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. N Engl J Med. 2021;385(18):1643-55.