Bölüm 13

ROMATOİD ARTRİT TANI VE TEDAVİSİ

Muhammed Recai AKDOĞAN[1]

GİRİŞ

Romatoid artrit (RA), etyolojisi net olarak bilinmeyen, sıklıkla küçük eklemler olmak üzere, tüm sinovyal eklemleri simetrik olarak tutabilen kronik, inflamatuar, otoimmün bir hastalıktır..Tüm dünyada RA görülme prevalansı %0,5-1 arasında bildirilirken, ülkemizde yapılan çalışmalarda bölgeler arası farklılık göstermektedir.[1-5] En yüksek prevelans %1 ile karadeniz bölgesinde, tüm bölgelerin dahil edildiğinde ise ortalama %0,56 olarak tespit edilmiştir.[1-5] RA, eklemlerde erozif hasar oluşturarak fonksiyon kaybına neden olurken, eşlik eden komorbid hastalıklar ve sistemik tutulumlar nedeni ile morbidite ve mortaliteye yol açar. RA'da erken dönemde yapılacak tedavi seçenekleri ile gelişebilecek sakatlıklar önlenebilir.

RA'nın kesin nedeni bilinmemekle birlikte, genetik yatkınlığı olan bireylerde çevresel faktörler, immün tetikleyicilerle hastalığın ortaya çıktığı düşünülmektedir.[6] RA'lı hastaların birinci derece yakınlarında hastalık görülme sıklığı artmıştır. Monozigotik ikizlerde hastalık görülme oranı %15-30, dizigotik ikizlerde %5 Tek yumurta ikizlerinde ise %12-15 olarak tesbit edilmiştir.[7] Bu nedenle hastalığın patogenezinde çevresel faktörlerin de katkısı olduğu düşünülmektedir. RA'da yatkınlık oluşturan çeşitli genler tanımlanmış ise de en sık HLA ilşkili genler suçlanmaktadır. HLA-DRB1*01, *04, *10, *14 allelleri RA ile ilişkili iken, HLA-DRB1*03, *07, *11, *13 alleri ise RA'ya karşı koruyucudur.[8] HLA lokusu dışında STAT4 (Transkripsiyon 4'ün sinyal transduser ve aktivatörü), PTPN2 (Protein tirozin fosfataz,nonreseptör Tip 2),PADI-4(Peptidilarginin deaminaz Tip 4) gibi genlerle de ilişkisi saptanmış. Çevresel faktörler sigara, mikrobiyota, silika tozu, hava kirliliği, enfeksiyonlar, hormonal faktörler, diyet ve alkol tüketimidir. RA kadınlarda daha sık görülmekte, kadın:erkek oranı 4:1, 4-5. dekatlarda pik yapmaktadır. Sigara RA ile ilişkisi kesinleşmiş risk faktörüdür. Sigara içmek veya antisiklik sitrüline peptid (anti-CCP) oluşumunu artırır. RA periodontal hastalıkla ilişkili, porphyromonas gingivalis, aggregatibacter suçlanmıştır. Hormonal

1 Arş. Gör., Dr., Atatürk Üniversitesi İç hastalıkları Ana Bilim Dalı, mrakdogan2163@gmail.com

TABLO 3: 2016 EULAR RA tedavi önerileri.	
A	RA hastalarının tedavisinde en iyi bakımın verilmesi hedeflenmelidir; tedavi, hasta ve romatolog arasındaki ortak bir karara dayandırılmalıdır
B	Tedavi kararı hastalık aktivitesine ve komorbiditeler, yapısal hasarın progresyonu ve güvenlik konuları gibi hasta ile ilişkili diğer faktörlere dayandırılmalıdır
C	Romatologlar, RA hastalarından primer sorumlu olması gereken uzmanlardır
D	RA bireysel, medikal ve toplumsal olarak yüksek maliyetlidir ve bunların hepsi tedaviyi veren romatolog tarafından göz önünde bulundurulmalıdır
1	RA tanısı konulur konulmaz DMARD'larla tedaviye başlanmalıdır
2	Tedavi, her hastada kalıcı remisyon veya düşük hastalık aktivitesine ulaşmayı amaçlamalıdır
3	Aktif hastalıkta izlem sık olmalıdır (her bir-üç ayda bir); tedavinin başlamasından sonra en geç üç ay içerisinde bir düzelme olmazsa veya hedefe altı ay içinde ulaşılamazsa tedavi yeniden düzenlenmelidir.
4	Metotreksat ilk tedavi stratejisinin bir parçası olmalıdır
5	Metotreksatın kontrendike olduğu hastalarda (veya erken intoleransta), leflunomid veya sülfasalazin (ilk) tedavi stratejisinin bir parçası olarak düşünülebilir
6	Kısa-süreli glukokortikoidlerin kullanımı, farklı doz ve uygulama yollarıyla, csDMARD'ların başlangıç veya değişiklik yapılan dönemlerinde düşünülmelidir, fakat klinik olarak mümkün olduğunda hızlıca azaltılması gerekmektedir
7	İlk csDMARD stratejisi ile tedavi hedefine ulaşılamazsa, kötü prognostik faktörlerin yokluğunda, diğer csDMARD'lar düşünülmelidir
8	İlk csDMARD stratejisi ile tedavi hedefine ulaşılamazsa, kötü prognostik faktörlerin varlığında, bir bDMARD veya tsDMARD eklenmesi düşünülmelidir, güncel pratik uygulama bir TNF inhibitörü ile başlamak şeklindedir
9	bDMARD ve tsDMARD bir csDMARD ile kombine edilmelidir; komedikasyon olarak csDMARD kullanamayan hastalarda, IL-6 yolağı inhibitörleri ve tsDMARD diğer bDMARD'larla karşılaştırıldığında bazı avantajlara sahip olabilir
10	Eğer bir bDMARD veya tsDMARD başarısız olursa, başka bir bDMARD veya tsDMARD'la tedavi düşünülmelidir; eğer bir TNF inhibitörü başarısız olursa, hastalar başka bir TNF inhibitörü veya farklı etki mekanizması olan bir ajan alabilir
11	Eğer glukokortikoidler azaltıldıktan sonra hastanın kalıcı remisyonu devam ediyorsa, özellikle bu tedavi csDMARD'larla kombine edilmiş ise, bDMARD'ların azaltılması düşünülebilir
12	Eğer hasta hâlâ kalıcı remisyonda ise csDMARD'ların azaltılması düşünülebilir

KAYNAKÇA

1.Smolen jS, Aletaha D, McInnes IB. Rheumatoid arthritis. lancet. 2016; 388: 2023-38.

2.Tobon Gj, Youinou p, Saraux A. The environment,geo-epidemiology, and autoimmunedisease: Rheumatoid arthritis. j Autoimmun.2010; 35: 104.

3.Akar S, Birlik M, Gurler o, et al. The prevalence of rheumatoid arthritis in an urban population of Izmir-Turkey. Clin Exp Rheumatol.2004; 22: 416-20.

4.Capkin E, Cakirbay H, Karkucak M, et al. prevalence of rheumatoid arthritis in the eastern Black Sea region of Turkey. Int j RheumDis. 2010; 13: 380-4.

5.Tuncer T, Gilgil E, Kacar C, et al. Prevalence of Rheumatoid Arthritis and Spondyloarthritis in Turkey: A nationwide Study. Arch Rheumatol. 2018; 33: 128-36.

6.MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum 2000;43(1):30-7.

7.McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. NEngl J Med2011;365(23):2205-19.

8.Konda Mohan V, Ganesan N, Gopalakrishnan R, Venkatesan V. HLA-DRB1 shared epitope alleles in patients with rheumatoid arthritis: relation to autoantibodies and disease severity in a South Indian population. Int J Rheum Dis 2017;20(10):1492-8.
9.Straub RH. The complex role of estrogens in inflammation. EndocrRev 2007;28(5):521-
10.Peschken CA, Robinson DB, Hitchon CA, Smolik I, Hart D, Bernstein CN, et al. Pregnancy and the risk of rheumatoid arthritis in a highly predisposed North American Native population. J Rheumatol 2012;39(12):2253-60.
11.Adab P, Jiang CQ, Rankin E, Tsang YW, Lam TH, Barlow J, et al. Breastfeeding practice, oral contraceptive use and risk of rheumatoid arthritis among Chinese women: the Guangzhou Biobank Cohort Study. Rheumatology (Oxford) 2014;53(5):860-6.
12.Whiting pF, Smidt n, Sterne jA, et al. Systematic review: accuracy of anti-citrullinated peptide antibodies for diagnosing rheumatoid arthritis. Ann Intern Med. 2010; 152: 456-64;W155-66.
13.Wilson A, Yu HT, Goodnough lT, nissensonAR. prevalence and outcomes of anemia inrheumatoid arthritis: a systematic review of the literature. Am j Med. 2004; 116 Suppl 7A:50S-7S.
14.Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315-24.
15.Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria:an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62(9):2569-81.
16.Radner H, neogi T, Smolen jS, Aletaha D.performance of the 2010 ACR/EUlAR classification criteria for rheumatoid arthritis: a systematic literature review. Ann Rheum Dis.2014; 73: 114-23.
17.Funovits J, Aletaha D, Bykerk V, Combe B, Dougados M, Emery P, et al. The 2010 American College of Rheumatology/European League against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I. Ann Rheum Dis2010;69(9):1589-95.
18.Neogi T, Aletaha D, Silman AJ, Naden RL, Felson DT, Aggarwal R, et al; ; EuropeanLeague Against Rheumatism. The 2010 American College of Rheumatology/European League against Rheumatism classification criteria for rheumatoid arthritis: phase 2 methodological report. Arthritis Rheum 2010;62(9):2582-91.
19.van der Linden MP, Knevel R, Huizinga TW, van der Helm-vanb Mil AH. Classification of rheumatoid arthritis: comparison of the 1987 American College of Rheumatology criteria and the 2010 American College of Rheumatology/European League AgainstRheumatism criteria. Arthritis Rheum 2011;63(1):37-42.
20.Raja R, Chapman PT, O'Donnell JL, Ipenburg J, Frampton C, Hurst M, et al. Comparison of the 2010 American College of Rheumatology/ european League Against Rheumatism and the 1987 American Rheumatism Association Classification Criteria for Rheumatoid Arthritis in an early arthritis cohort in New Zealand. J Rheumatol 2012;39(11):2098-103.
21.Biliavska I, Stamm TA, Martinez-Avila J, Huizinga TW, Landewé RB, Steiner G, et al.Application of the 2010 ACR/EULAR classification criteria in patients with very early inflammatory arthritis: analysis of sensitivity, specificity and predictive values in the SAVE study cohort. Ann Rheum Dis 2013;72(8):1335-41.
22.Radner H, Neogi T, Smolen JS, Aletaha D. Performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: a systematic literature review. Ann Rheum Dis 2014;73(1):114-23.
23.Kennish L, Labitigan M, Budoff S,Filopoulos MT, Mc Cracken WA, Swearingen CJ, et al. Utility of the new rheumatoid arthritis 2010 ACR/EULAR classification criteria in routine clinical care. BMJ Open 2012;2:e001117.
24.Berglin E, Dahlqvist SR. Comparison of the 1987 ACR and 2010 ACR/EULAR classification criteria for rheumatoid arthritis in clinical practice: a prospective cohort study. Scand J Rheumatol 2013;42(5):362-8.

25.Vonkeman HE, van de Laar MA. The new European League Against Rheumatism/American College of Rheumatology diagnostic criteria for rheumatoid arthritis: how are they performing? Curr Opin Rheumatol 2013;25(3):354-9.
26.Zhao J, Su Y, Li R, Ye H, Zou Q, Fang Y, et al. Classification criteria of early rheumatoid arthritis (ERA) and validation of its performance in amulti-centre cohort. Clin Exp Rheumatol 2014;32(5):667-73.
27.Ye H, Su Y, Li R, Zhao J, Liu X, Mei Y, et al. Comparison of three classification criteria of rheumatoid arthritis in an inception early arthritis cohort. Clin Rheumatol 2016;35(10):2397-401.
28.Geraldino-Pardilla L. Management of rheumatoid arthritis: Synovitis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Michael H. Weisman MH, eds. Rheumatology. 6th ed. Philadelphia: Elsevier Mosby; 2014. p.802-8.
29.Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M,Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann RheumDis 2016;75(1):3-15.
30.Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 2004;364(9430):263-9.
31.Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73(3):492-509.
32.Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis.Arthritis Rheum 1995;38(1):44-8.
33.Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eber G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology 2003;42(2):244-57.
34.Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Rheumatol 2005;23(5 Suppl 39):S100-8.
35.Crofford LJ. Use of NSAIDs in treating patients with arthritis. Arthritis Research & Therapy. 2013;15(Suppl 3):S2. doi:10.1186/ar4174.
36.Peng S, Duggan A. Gastrointestinal adverse effects of non-steroidal antiinflammatory drugs. Expert Opin Drug Saf. 2005;4:157-69.
37.Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med1995;333(3):142-6.
38.Kenneth G. Saag FB. Systemic glucocorticoids in rheumatology.In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Michael H. Weisman MH, eds. Rheumatology. 6th ed. Philadelphia: Elsevier Mosby; 2014. p.423-33.
39.Gorter SL, Bijlsma JW, Cutolo M, Gomez-Reino J, Kouloumas M,Smolen JS, et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69(6):1010-4.
40.Fautrel B, Mitrovic S, Taylor P. Treatment of rheumatoid arthritis. EULAR course on line on Rheumatic Diseases. 2017.
41.Gaujoux-Viala C, Nam J, Ramiro S, Landewé R, Buch MH, Smolen JS, et al. Efficacy of conventional synthetic disease-modifying anti rheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2014;73(3):510-5.
42.Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: Drug-exposure limitations of

oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration. Ann Rheum Dis 2014;73(8):1549-51.
43.Fonseca JE, Taylor P. Rheumatoid arthritis: Treatment. In: BijlsmaJWJ, Hachulla E;European League against Rheumatism. eds. EULAR Textbook on Rheumatic Diseases. 2nd ed. London: BMJ Publishing; 2015. p.265-94.
44.Johnsen AK. Methotrexate. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Michael H. Weisman MH, eds. Rheumatology. 6th ed. Philadelphia: Elsevier Mosby; 2014. p.443-9.
45.Haraoui. B. Leflunomide. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Michael H. Weisman MH, eds. Rheumatology. 6th ed. Philadelphia: Elsevier Mosby; 2014. p.451-7.
46.Hochberg MC, Gravallese EM, Silman AJ, Smolen JS, Michael E Weinblatt ME, eds. Rheumatology. eBook. 7th ed. Philadelphia, PA: Elsevier; 2019. p. 1808.
47.Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. European Leflunomide Study Group. Lancet 1999;353(9149):259-66.
48.Cohen S, Cannon GW, Schiff M, Weaver A, Fox R, Olsen N, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of leflunomide in the treatment of Rheumatoid Arthritis Trial İnvestigator Group. Arthritis Rheum 2001;44(9):1984-92.
49.Duncan MR, Capell HA. The use of antimalarials in combination with other disease modifying agents in RA--the British experience. Lupus 1996;5(Suppl 1):S50-8.
50.Bykerk VP. Non-immunsupressive disease-modifying anti-rheumatic drugs. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Michael H. Weisman MH, eds. Rheumatology. 6th ed. Philadelphia: Elsevier Mosby; 2014. p. 434-42.
51.Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF; American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology 2016;123(6):1386-94.
52.Bird HA. Sulphasalazine, sulphapyridine or 5-aminosalicylic acid--which is the active moiety in rheumatoid arthritis? Br J Rheumatol 1995;34(Suppl 2):16-9.
53.Ardıçoğlu Ö. [Treatment of rheumatoid arthritis]. In: Ataman Ş, Yalçın P, editörler. Romatoloji. Yenişehir/Ankara: MN Medikal & Nobel; 2012. p.531-8.
54.Bykerk VP. Non-immunsupressive disease-modifying anti-rheumatic drugs. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Michael H. Weisman MH, eds. Rheumatology. 6th ed. Philadelphia: Elsevier Mosby; 2014. p. 434-42.
55.Radner H, Aletaha D. Anti-TNF in rheumatoid arthritis: an overview. Wien Med Wochenschr. 2015;165:3-9.
56.Knight DM, Trinh H, Le J, Siegel S, Shealy D, McDonough M,et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol 1993;30(16):1443-53.
57.Machado MA, Maciel AA, de Lemos LL, Costa JO, Kakehasi AM, Andrade EI, et al. Adalimumab in rheumatoid arthritis treatment: a systematic review and meta-analysis of randomized clinical trials. Rev Bras Reumatol 2013;53(5):419-30.
58.Pasut G. Pegylation of biological molecules and potential benefits: pharmacological properties of certolizumab pegol. BioDrugs. 2014;28 Suppl 1:S15-23.
59.Keystone E, Heijde D, Mason D, Jr, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo controlled, parallel-group study. Arthritis Rheum. 2008;58:3319-29.
60.Ling J, Lyn S, Xu Z, et al. Lack of racial differences in the pharmacokinetics of subcutaneous golimumab in healthy Japanese and Caucasian male subjects. J Clin Pharmacol. 2010;50:792-802.
61.Thalayasingam N, Isaacs JD. Anti-TNF therapy. Best Pract Res Clin Rheumatol 2011;25(4):549-67.

62.Blair HA, Deeks ED. Abatacept: a review in rheumatoid arthritis. Drugs 2017;77(11):1221-33.
63.Schiff M. Subcutaneous abatacept for the treatment of rheumatoid arthritis. Rheumatology (Oxford) 2013;52(6):986-97.
64.Schiff M, Weinblatt ME, Valente R, van der Heijde D, Citera G, Elegbe A, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis 2014;73(1):86-94.
65.Isaacs JD, Cohen SB, Emery P, Tak PP, Wang J, Lei G, et al. Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. Ann Rheum Dis 2013;72(3):329-36.
66.Lal P, Su Z, Holweg CT, Silverman GJ, Schwartzman S, Kelman A, et al. Inflammation and autoantibody markers identify rheumatoid arthritis patients with enhanced clinical benefit following rituximab treatment. Arthritis Rheum 2011;63(12):3681-91.
67.van Vollenhoven RF, Emery P, Bingham CO 3rd, Keystone EC, Fleischmann RM, Furst DE, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Annals of the Rheumatic Diseases 2013;72(9):1496-502.
68.Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dörner T, et al; Rituximab Consensus Expert Committee. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70(6):909-20.
69.Cohen MD, Keystone E. Rituximab for rheumatoid arthritis. RheumatolTher 2015;2(2):99-111.
70.Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004;350(25):2572-81.
71.Leandro MJ (author), Maini RN (section editor), Romain PL (deputy editor). Rituximab and other B cell targeted therapies for rheumatoid arthritis. UpToDate 2017.https://www.uptodate.com/contents/rituximab-and-other-b-cell-targeted-therapies-for-rheumatoid-arthritis 72.Agency. EM.Mabthera.http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000165/human_med_000897.jsp&mid=WC0b01ac058001d124 (10.02.2018)
73.Strangfeld A, Richter A, Siegmund B, Herzer P, Rockwitz K, Demary W, et al. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. Ann Rheum Dis 2017;76(3):504-10.
74.Kettle JG, Åstrand A, Catley M, Grimster NP, Nilsson M, Su Q, et al. Inhibitors of JAK-family kinases: an update on the patent literatüre 2013-2015, part 1. Expert Opin Ther Pat 2017;27(2):127-43.
75.Boyle DL, Soma K, Hodge J, Kavanaugh A, Mandel D, Mease P, et al. The JAK inhibitor tofacitinib suppresses synovial JAK1-STAT signalling in rheumatoid arthritis. Ann Rheum Dis 2015;74(6):1311-6.
76.Fleischmann R, Kremer J, Tanaka Y, Gruben D, Kanik K, Koncz T, et al. Efficacy and safety of tofacitinib in patients with active rheumatoid arthritis: review of key Phase 2 studies. Int J Rheum Dis 2016;19(12):1216-25.
77.Yamaoka K. Janus kinase inhibitors for rheumatoid arthritis. Curr Opin Chem Biol 2016;32:29-33.
78.Strand V, Ahadieh S, French J, Geier J, Krishnaswami S, Menon S, et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. Arthritis Res Ther 2015;17:362.
79.Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated rheumatoid arthritis patients. Ann Rheum Dis 2016;75(10):1843-7.
80.Blair HA. Gp2013: a rituximab biosimilar. BioDrugs 2017;31(5):465-8.
81.Jamshidi A, Gharibdoost F, Vojdanian M, Soroosh SG, Soroush M, Ahmadzadeh A, et al. A phase III, randomized, two-armed, double-blind, parallel, active controlled, and non-inferio-

rity clinical trial to compare efficacy and safety of biosimilar adalimumab (CinnoRA®) to the reference product (Humira®) in patients with active rheumatoid arthritis. Arthritis Res Ther 2017;19(1):168.

82. Emery P, Vencovský J, Sylwestrzak A, Leszczyński P, Porawska W, Baranauskaite A, et al. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis 2017;76(1):51-7.
83. Komaki Y, Yamada A, Komaki F, Kudaravalli P, Micic D, Ido A, et al. Efficacy, safety and pharmacokinetics of biosimilars of anti-tumor necrosis factor-α agents in rheumatic diseases; a systematic review and meta-analysis. J Autoimmun 2017;79:4-16.
84. Ruiz-Argüello MB, Maguregui A, Ruiz Del Agua A, Pascual-Salcedo D, Martinez-Feito A, Jurado T, et al. Antibodies to infliximab in remicade-treated rheumatic patients show identical reactivity towards biosimilars. Ann Rheum Dis 2016;75(9):1693-6.