

COVID-19 PATOFİZYOLOJİSİ VE TEDAVİDE KULLANILAN ROMATOLOJİK İLAÇLAR

Deniz ÇEKİÇ¹
Emel GÖNÜLLÜ²

GİRİŞ

Koronavirüs 1949 yılından beri bilinen, sıklıkla üst solunum yolu enfeksiyonu ve pnömoniye yol açan, tek zincirli yaklaşık 60 nm boyutunda mRNA virüsüdür[1]. Virüsün virülans faktörleri, taç şeklinde olan 3'lü spike (S) glikoproteini hücre membranına tutunmayı sağlamaktadır, virüsün diğer virülans faktörleri birer glikoprotein olan membran (M), zarf (Z) ve nükleokapsid (N) proteinleridir[2]. Doğal konakları insan ve diğer memeliler (deve, köpek, domuz, kedi) başta olmak üzere tavuk ve kuşlardır. Koronavirüsler, dünyada son 2 yüzyılda 3 kez ciddi hastalıklara yol açmıştır. İlki 2002 yılında yine Çin'de başlayarak SARS'a (ciddi akut solunum yolu hastalığı) yol açmış 4 ülkeye yayılmıştır ve bilinen 774 ölüme sebep olmuştur[1,3]. Diğer 2012 yılında MERS (ortadoğu solunum sendromu) develerden bulaştığı tahmin edilmektedir; 858 kişinin ölümüne sebep olmuştur ve 24 ülkeye yayılmıştır [4]. Aralık 2019'da ise yine Çin'de yeni bir koronavi-

rüs salgını başlamıştır (novel-coronavirus/SARS-Cov-2) Mart 2020 de ise Dünya Sağlık Örgütü (DSÖ) tarafından COVID-19 pandemisi ilan edilmiştir[5]. COVID-19'a neden olan koronavirüsün yarasalardan kaynaklandığı düşünülmekle beraber pangolin gibi ara konaklarının olduğu da düşünülmektedir[6]. On Ocak 2021 tarihi ile 10 aydır devam etmekte olan pandemide 90.429.982 vaka bildirilmiş olup 1.939.639 kişinin ölümüne sebep olmuştur[7]. Bulaşma şekli hasta kişilerin sekresyonlarının damlacık yoluyla sağlam kişilere geçmesiyle olmaktadır. Virüsün paslanmaz çelik gibi yüzeylerde 30 güne kadar canlı kalabildiği ancak virülansının azaldığı bilinmektedir. Hali hazırda bilinen en iyi koruyucu yöntem, en az 2 metrelik sosyal mesafe, maske kullanımı ve kişisel hijyen olarak gösterilmektedir[8].

Klinik olarak COVID-19 hastalarının hastaneye başvuru sebeplerine bakıldığında en sık ateş, öksürük, balgam, nefes darlığı, halsizlik, olfaktör sinir etkilenmesi ile koku kaybı olarak görülmektedir[9]. Virüsle karşılaşma olduktan sonra klinik

¹ Uzm. Dr., Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi, decekic@gmail.com

² Prof. Dr., Sakarya Üniversitesi Eğitim Araştırma Hastanesi İç Hastalıkları Romatoloji Bilim Dalı, emelorge@yahoo.com

KAYNAKÇA

- Groupe V. Demonstration of an interference phenomenon associated with infectious bronchitis virus of chickens. *J Bacteriol.* 1949;58: 23–32.
- King AMQ, Adams MJ, Lefkowitz EJ. *Virus Taxonomy: Classification and Nomenclature of Viruses : Ninth Report of the International Committee on Taxonomy of Viruses.* Elsevier; 2011.
- Severe Acute Respiratory Syndrome (SARS). [cited 10 Jan 2021]. Available: https://www.who.int/health-topics/severe-acute-respiratory-syndrome#tab=tab_1
- Middle East respiratory syndrome coronavirus (MERS-CoV). [cited 10 Jan 2021]. Available: https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus-mers#tab=tab_1
- Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed.* 2020;91: 157–160.
- Lam TT-Y, Jia N, Zhang Y-W, Shum MH-H, Jiang J-F, Zhu H-C, et al. Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature.* 2020. pp. 282–285. doi:10.1038/s41586-020-2169-0
- Coronavirus Update (Live): 90,429,982 Cases and 1,939,630 Deaths from COVID-19 Virus Pandemic - Worldometer. [cited 10 Jan 2021]. Available: <https://www.worldometers.info/coronavirus/>
- Coronavirus Disease (COVID-19) Situation Reports. [cited 11 Jan 2021]. Available: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>
- Yegorov S, Goremykina M, Ivanova R, Good SV, Babenko D, Shevtsov A, et al. Epidemiological and Clinical Characteristics, and Virologic Features of COVID-19 Patients in Kazakhstan: a Nation-Wide, Retrospective, Cohort Study. doi:10.1101/2021.01.06.20249091
- He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med.* 2020;26: 672–675.
- Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. *Eur Radiol.* 2020;30: 4381–4389.
- Zhang X, Li S, Niu S. ACE2 and COVID-19 and the resulting ARDS. *Postgrad Med J.* 2020;96: 403–407.
- Chen Z, Zhang F, Hu W, Chen Q, Li C, Wu L, et al. Laboratory markers associated with COVID-19 progression in patients with or without comorbidity: A retrospective study. *J Clin Lab Anal.* 2020; e23644.
- Li S-R, Tang Z-J, Li Z-H, Liu X. Searching therapeutic strategy of new coronavirus pneumonia from angiotensin-converting enzyme 2: the target of COVID-19 and SARS-CoV. *Eur J Clin Microbiol Infect Dis.* 2020;39: 1021–1026.
- Jaimes JA, Millet JK, Whittaker GR. Proteolytic Cleavage of the SARS-CoV-2 Spike Protein and the Role of the Novel S1/S2 Site. *iScience.* 2020;23: 101212.
- Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clinical Rheumatology.* 2020. pp. 2085–2094. doi:10.1007/s10067-020-05190-5
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395: 497–506.
- McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *The Lancet Rheumatology.* 2020;2. doi:10.1016/S2665-9913(20)30121-1
- Vasquez-Bonilla WO, Orozco R, Argueta V, Sierra M, Zambrano LI, Muñoz-Lara F, et al. A review of the main histopathological findings in coronavirus disease 2019. *Hum Pathol.* 2020;105. doi:10.1016/j.humpath.2020.07.023
- Sinha P, Matthay MA, Calfee CS. Is a “Cytokine Storm” Relevant to COVID-19? *JAMA Intern Med.* 2020;180. doi:10.1001/jamainternmed.2020.3313
- Bilgin E, Ertenli Aİ. Proposal of a new nomenclature for the underlying pathogenetic mechanism of severe Coronavirus Disease-19: “Inflammatory Thrombosis with Immune Endotheliitis-ITIE.” *Rheumatol Int.* 2021 [cited 23 Jan 2021]. doi:10.1007/s00296-020-04768-1
- Pine AB, Meizlish ML, Goshua G, Chang CH, Zhang H, Bishai J, et al. Circulating markers of angiogenesis and endotheliopathy in COVID-19. *Pulm Circ.* 2020;10. doi:10.1177/2045894020966547
- Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA.* 2020;324: 782–793.
- Bohn MK, Hall A, Sepiashvili L, Jung B, Steele S, Adeli K. Pathophysiology of COVID-19: Mechanisms Underlying Disease Severity and Progression. *Physiology .* 2020;35: 288–301.
- Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest.* 2009;39: 618–625.
- Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med.* 2020;382: 929–936.

27. Fraga-Silva RA, Sorg BS, Wankhede M, Dedeugd C, Jun JY, Baker MB, et al. ACE2 activation promotes antithrombotic activity. *Mol Med*. 2010;16: 210–215.
28. White NJ. The treatment of malaria. *N Engl J Med*. 1996;335: 800–806.
29. Mauthe M, Orhon I, Rocchi C, Zhou X, Luhr M, Hijlkema K-J, et al. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. *Autophagy*. 2018;14: 1435–1455.
30. Khan M, Santhosh SR, Tiwari M, Lakshmana Rao PV, Parida M. Assessment of in vitro prophylactic and therapeutic efficacy of chloroquine against Chikungunya virus in vero cells. *J Med Virol*. 2010;82: 817–824.
31. Delvecchio R, Higa LM, Pezzuto P, Valadão AL, Garcez PP, Monteiro FL, et al. Chloroquine, an Endocytosis Blocking Agent, Inhibits Zika Virus Infection in Different Cell Models. *Viruses*. 2016;8. doi:10.3390/v8120322
32. Dowall SD, Bosworth A, Watson R, Bewley K, Taylor I, Rayner E, et al. Chloroquine inhibited Ebola virus replication in vitro but failed to protect against infection and disease in the in vivo guinea pig model. *J Gen Virol*. 2015;96: 3484–3492.
33. Meo SA, Klonoff DC, Akram J. Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19. *Eur Rev Med Pharmacol Sci*. 2020;24: 4539–4547.
34. Search of: chloroquine. [cited 13 Jan 2021]. Available: <https://www.clinicaltrials.gov/ct2/results?term=chloroquine&cond=COVID19>
35. Self WH, Semler MW, Leither LM, Casey JD, Angus DC, Brower RG, et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324: 2165–2176.
36. Mahévas M, Tran V-T, Roumier M, Chabrol A, Paule R, Guillaud C, et al. Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ*. 2020;369: m1844.
37. Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai M-C. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review. *Heart Rhythm*. 2020;17: 1472–1479.
38. Das RR, Jaiswal N, Dev N, Jaiswal N, Naik SS, Sankar J. Efficacy and Safety of Anti-malarial Drugs (Chloroquine and Hydroxy-Chloroquine) in Treatment of COVID-19 Infection: A Systematic Review and Meta-Analysis. *Front Med*. 2020;7: 482.
39. Coronavirus disease (COVID-19): Hydroxychloroquine. [cited 13 Jan 2021]. Available: <https://www.who.int/news-room/q-a-detail/coronavirus-disease-COVID-19-hydroxychloroquine>
40. Burns CM. The History of Cortisone Discovery and Development. *Rheum Dis Clin North Am*. 2016;42: 1–14, vii.
41. Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. *Am J Med*. 1977;63: 200–207.
42. Meduri GU, Headley S, Tolley E, Shelby M, Stentz F, Postlethwaite A. Plasma and BAL cytokine response to corticosteroid rescue treatment in late ARDS. *Chest*. 1995;108: 1315–1325.
43. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1998;280: 159–165.
44. [No title]. [cited 13 Jan 2021]. Available: <http://www.ijcem.com/files/ijcem0020929.pdf>
45. Search of: corticosteroid. [cited 14 Jan 2021]. Available: <https://www.clinicaltrials.gov/ct2/results?cond=COVID19&term=corticosteroid&cntry=&state=&city=&dist=>
46. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, García-Ibarbia C, et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. *medRxiv*. 2020; 2020.06.17.20133579.
47. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with COVID-19 - Preliminary Report. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2021436
48. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod Rheumatol*. 2009;19: 12–19.
49. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. *Ann Rheum Dis*. 2007;66: 1162–1167.
50. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. *Autoimmun Rev*. 2020;19: 102537.
51. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with

- tocilizumab. *Proc Natl Acad Sci U S A*. 2020;117: 10970–10975.
52. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. *Autoimmun Rev*. 2020;19: 102568.
 53. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in Patients Hospitalized with COVID-19 Pneumonia. *N Engl J Med*. 2021;384: 20–30.
 54. COVID-19: Studio randomizzato italiano, nessun beneficio dal tocilizumab. [cited 23 Jan 2021]. Available: <https://www.aifa.gov.it/web/guest/-/COVID-19-studio-randomizzato-italiano-nessun-beneficio-dal-tocilizumab>
 55. Sepriano A, Kerschbaumer A, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2020;79. doi:10.1136/annrheumdis-2019-216653
 56. Cortegiani A, Ippolito M, Greco M, Granone V, Protti A, Gregoretti C, et al. Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review. *Pulmonology*. 2021;27. doi:10.1016/j.pulmoe.2020.07.003
 57. Huizinga TWJ, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, et al. Sarilumab, a fully human monoclonal antibody against IL-6R α in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. *Ann Rheum Dis*. 2014;73: 1626–1634.
 58. Search of: sarilumab. [cited 14 Jan 2021]. Available: <https://www.clinicaltrials.gov/ct2/results?cond=COVID19&term=sarilumab&cntry=&state=&city=&dist=>
 59. Benucci M, Giannasi G, Cecchini P, Gobbi FL, Damiani A, Grossi V, et al. COVID-19 pneumonia treated with Sarilumab: A clinical series of eight patients. *Journal of medical virology*. 2020. pp. 2368–2370.
 60. Tutuncu Z K. A. Anticytokine therapies. In: Firestein GS, In: Budd RC, Gabriel SE, McInnes IB, O'Dell JR, editors, editor. *Kelley's textbook of rheumatology 9th ed Philadelphia: Elsevier; 2013. pp. 957–77.*
 61. Conti P, Ronconi G, Caraffa A, Gallenga C, Ross R, Frydas I, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents*. 2020;34: 327–331.
 62. Search of: anakinra. [cited 14 Jan 2021]. Available: <https://www.clinicaltrials.gov/ct2/results?cond=COVID19&term=anakinra&cntry=&state=&city=&dist=>
 63. Dimopoulos G, de Mast Q, Markou N, Theodorakopoulou M, Komnos A, Mouktaroudi M, et al. Favorable Anakinra Responses in Severe COVID-19 Patients with Secondary Hemophagocytic Lymphohistiocytosis. *Cell Host Microbe*. 2020;28: 117–123.e1.
 64. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol*. 2020;2: e325–e331.
 65. Galeotti C, Kaveri SV, Bayry J. IVIG-mediated effector functions in autoimmune and inflammatory diseases. *Int Immunol*. 2017;29: 491–498.
 66. Hung IFN, To KKW, Lee C-K, Lee K-L, Yan W-W, Chan K, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. *Chest*. 2013;144: 464–473.
 67. Cao W, Liu X, Bai T, Fan H, Hong K, Song H, et al. High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019. *Open Forum Infect Dis*. 2020;7: ofaa102.
 68. Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. *The Journal of infection*. 2020. pp. 318–356.
 69. Pei L, Zhang S, Huang L, Geng X, Ma L, Jiang W, et al. Antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin in 1142 patients with coronavirus disease 2019: a systematic review and meta-analysis. *Polish archives of internal medicine*. 2020;130. doi:10.20452/pamw.15543
 70. Gracheva IA, Shchegrovina ES, Schmalz H-G, Betsltskaya IP, Fedorov AY. Colchicine Alkaloids and Synthetic Analogues: Current Progress and Perspectives. *J Med Chem*. 2020;63: 10618–10651.
 71. van den Berg DF, Te Velde AA. Severe COVID-19: NLRP3 Inflammasome Dysregulated. *Front Immunol*. 2020;11: 1580.
 72. Search of: colchicine. [cited 14 Jan 2021]. Available: <https://www.clinicaltrials.gov/ct2/results?cond=COVID19&term=colchicine&cntry=&state=&city=&dist=>
 73. Deftereos SG, Siasos G, Giannopoulos G, Vrachatis DA, Angelidis C, Giotaki SG, et al. The Greek study in the effects of colchicine in COVID-19 complications prevention (GRECCO-19 study): Rationale and study design. *Hellenic J Cardiol*. 2020;61: 42–45.