Monoclonal Antibodies for COVID-19 Treatment: Is It an Option in Indonesia?

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More than three years after the emergence of Coronavirus disease 2019 (COVID-19), an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV2), was declared a pandemic by the World Health Organization, reports of COVID-19 hospitalization and death have begun decreasing. Even though COVID-19 as a global health emergency has been declared over, research in finding and evaluating modalities that can decrease severity and mortality from COVID-19 infection are still on going.[1] To date, there have been more than 380,000 publications on Pubmed under the search term "COVID 19". Excessive inflammatory activation is an important part of COVID-19 pathogenesis which is caused by interaction of the virus with the host and modulation of the host's immune response.[2] Better understanding of COVID-19 pathogenesis could improve the strategies used to manage COVID-19 infection. Monoclonal antibodies are one treatment modality that can be used to target the virus itself or modulate the dysregulated immune response in COVID-19. Monoclonal antibodies (mAbs) can halt progression of COVID-19 in high-risk patients. However, considering the limited production and high cost, is this treatment modality an option in Indonesia?

Even though most COVID-19 cases are mild or moderate and restricted to the upper airways, some cases can progress to life-threatening pneumonia. This has caused more than 160,000 deaths in Indonesia and six million deaths worldwide.[3,4] SARS-COV2 has a set of non-structural proteins, structural proteins (spike glycoprotein, membrane protein, nucleocapsid protein, and envelope protein), and accessory proteins. The spike glycoprotein is the main determinant for this virus tropism.[3] The spike protein is the main antigenic part which binds to host cell receptors, facilitates viral invasion of host cells, and stimulates immune responses.[5] The spike protein has two subunits: the S1 and S2 subunits. The S1 subunit binds to the angiotensin-converting enzyme 2 (ACE2) receptor, while the S2 subunit mediates membrane fusion. After binding to ACE2, the spike protein is cleaved by transmembrane serine protease (TMPRSS).[3] Pattern recognition receptors (PRRs) detect danger-associated molecular patterns (DAMPs) that indicate the disturbance of host homeostasis and pathogen-associated molecular patterns (PAMPs) from the virus.[2,5] This condition could induce cytokines downstream.[2] Adequate and synchronized innate and adaptive immunity are needed for a good antiviral immune response.6 To adapt to human cells as a new environment, the SARS-COV2 virus can modify its ribonucleic acid (RNA), antagonize and escape immune responses, and induce apoptosis of immune cells which can lead to immune system dysregulation.[5] Multisystemic immune dysregulation appears in critically ill COVID-19 patients and is triggered by viral molecules and extensive

tissue damage. Hyperactivation of neutrophils and infiltrating macrophages lead to excessive cytokine expression or cytokine storm which can activate endothelial and epithelial tissues. Proinflammatory cytokines, such as interleukin-6 (IL-6), IL-17, IL-8, interferon gamma (IFN gamma), and tumor necrosis factor alpha (TNF alpha), correlate with disease severity. A hyperinflammatory microenvironment leads to functional impairment of antiviral lymphocytes.[2]

There are some strategies currently available to fight SARS-COV-2 infection, namely targeting the virus itself or targeting the pathological inflammatory response.[2] To decrease COVID-19 associated mortality, approaches do not only focus on hospitalized patients, but also on suppressing the viral replication to prevent progression to a hyperinflammatory condition that can cause severe COVID-19 cases among ambulatory high-risk patients. Studies on finding new treatments or re-purposing the use of old drugs have been conducted since the early days of the COVID-19 pandemic with the aim of improving patient outcomes. Significant developments have been made and there are a variety of novel therapeutic options, including antiviral drugs, immunomodulatory treatments, and mAbs, for the management of COVID-19. However, these drugs have shown limited therapeutic potential and effectivity depends on the stage of the illness.[7]

In this issue, we have a systematic review and meta-analysis conducted by Wafa et al from Airlangga University assessing the efficacy and safety of mAb treatments against COVID-19. Using predefined search criteria, they conducted systematic searching from January 2021 to March 2021 which identified sixteen randomized control trials (RCTs) and eleven of these RCTs were found to have a low risk of bias. This meta-analysis had 4700 participants in the intervention group and 4157 participants in the control group and assessed the effect of mAbs on the following: COVID-19 treatment for all-cause mortality, the need for mechanical ventilation, hospital discharge at day 28-30, change in viral load, and serious adverse events. The monoclonal antibodies included in this meta-analysis were anti-spike mAbs (bamlanivimab monotherapy, bamlanivimab-etesevimab, casirivimab-imdevimab (REGN-COV2), anti-IL-6 (tocilizumab and sarilumab), and anti-C5a (Vilobelimab/IFX-1). This meta-analysis found that tocilizumab reduced the mortality risk in severe to critical COVID-19 patients as well as the need for mechanical ventilation, and increased the incidence of hospital discharge at day 28-30. Bamlanivimab monotherapy did not reduce mortality nor viral load. It also did not increase the hospital discharge rate. Meanwhile, bamlanivimab-etesevimab and REGN-COV2 significantly decreased viral load. No mortality risk reduction was seen with Vilobelimab. For all the mAbs included in the meta-analysis, no major safety concern was documented.[8]

Monoclonal antibodies are antibodies developed from a single cell lineage that has a high affinity for its target cell. Monoclonal antibodies have been used in various conditions from before the onset of the COVID-19 pandemic, namely malignancy, autoimmune diseases, transplantation, and also other infectious diseases.[7] There are two mechanisms of mAbs used in COVID-19 management: modulating hyperinflammatory conditions and targeting spike protein.[9]

Tocilizumab and sarilumab are both anti–IL-6 mAbs and they received emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA) in June 2021 for COVID-19 patients who were hospitalized with COVID-19, receiving corticosteroid and requiring supplemental oxygen. IL-6 blockade can attenuate the hyperinflammatory response to SARS-CoV-2.[9,10] Modulating the levels of proinflammatory IL-6 may decrease the duration and severity of COVID-19.[11] Before the COVID-19 pandemic, these mAbs had been approved for treatment of inflammatory conditions, such as rheumatoid arthritis.[9] The Infectious Diseases Society of America (IDSA) recommends the addition of tocilizumab to the standard of care for hospitalized adult COVID-19 patients with progressive, severe or critical conditions (on mechanical ventilation or have end-organ dysfunction) who have elevated markers of systemic inflammation. If tocilizumab is not available, sarilumab might be an alternative

for this kind of patient. In Indonesia, tocilizumab is available and listed in the national drug standard (formularium) for rheumatoid arthritis.[12]

Monoclonal antibodies targeted towards the receptor binding domain (RBD) of the spike protein and multiple epitopes of the S protein are used to neutralize COVID-19 infection.[13] For antiviral function, mAb has a better safety profile and more specific target than polyclonal antibodies used for infectious diseases.[7] Bamlanivimab, an mAb which binds to the receptor binding domain (RBD), at first received an EUA from the FDA as monotherapy based on interim results from the trial. Subsequent results from that same trial then led to the approval of combination treatment with etesevimab. Etesevimab is a neutralizing antibody that binds to a region in the RBD that overlaps with the region that bamlanivimab targets.[9] Bamlanivimab is not so effective against most of the COVID-19 variants, but its efficacy is improved when in combination with etesevimab. The FDA then cancelled the EUA for bamlanivimab as monotherapy.[13]

The FDA issued EUA for bamlanivimab/etesevimab, sotrovimab, and casirivimab/imdevimab in December 2021 for non-hospitalized immunosuppressed COVID-19 patients who are at high risk of progression. Some of the high-risk conditions cited are being 65 years old or more; having underlying diabetes mellitus (DM), chronic kidney disease (CKD), or immunosuppressive disease; a body mass index (BMI) ≥ 35 kg/m; being on immunosuppressive therapy; and being more than 55 years of age and having hypertension, cardiovascular disease, or a chronic respiratory disease. These mAbs are not authorized for use in patients who require oxygen therapy due to COVID-19 and patients with known hypersensitivity to any of its ingredients.[7,9]

Bamlanivimab/etesevimab and casirivimab/imdevimab work by binding to the RBD, while sotrovimab binds to the S2 subunit. The S2 subunit, which is conserved in SARS-CoV-2 across variants, helps the fusion of virus and host membrane. Because of this, the only monoclonal antibody considered effective against the omicron variant, as of January 2022, is sotrovimab.[9] IDSA recommends anti–SARS-CoV-2 monoclonal antibodies with activity against the predominant regional variants within seven days of symptom onset for ambulatory patients or patients admitted to the hospital for reasons other than COVID-19, who have mild-to-moderate COVID-19 and are at high risk of progression to severe disease.[12]

The monoclonal antibody that targets the spike protein and received EUA for COVID-19 management from The Indonesian Food and Drug Authority is regdanvimab. Regdanvimab neutralizes the receptor-binding site of the SARS-CoV-2 spike protein as an antigen target. On March 2021, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) concluded that regdanvimab, which had not received EUA from FDA, could be used for adult patients with COVID-19 who do not require supplemental oxygen but are at high risk of progression to severe disease. Regdanvimab is indicated for high-risk mild and all moderate COVID-19 patients. High risk conditions include an age of more than 50 years, cardiovascular disease (including hypertension), BMI of more than 30 kg/m^2, DM, chronic lung disease, chronic liver disease, CKD, and immunosuppression due to disease or treatment.[14]

The rapid development of mAb treatment for COVID-19 has been an impressive achievement.[15] The use of mAbs in COVID-19 treatment has also been recommended in the Indonesian guidelines for COVID-19 management.[16] However, this approach has some limitations. First, the genomic variability and high infectivity of SARS-CoV-2 can result in high antigenic variation which can lead to mAbs resistance before or after treatment. This resistance might render mAbs ineffective in treating COVID-19 infection. Resistance before treatment discourages regulatory bodies from introducing a mAb into guidelines when the prevalence of the mutations that have initial resistance to the mAb in the circulating strains is high. Secondly, the cost of production of mAbs is high which makes the availability of this treatment option limited in low to middle income countries.[15] The estimated price for bamlanivimab/etesevimab and casirivimab/imdevimab is around $2,400, while regdanvimab

is approximately $446.[17]

Many things have been learned from this pandemic and serve as lessons for preparing for the next pandemic or other emerging diseases. Various therapeutic developments to treat COVID-19 have been studied for both hospitalized patients and in outpatient settings. One of these developments is the use of a variety of monoclonal antibodies that have shown overall moderate efficacy in decreasing severity and mortality from COVID-19 infection and also good safety.[9] Unfortunately, besides the variable efficacy across variants, the cost for monoclonal antibodies (mAbs) is still high which potentially makes access to this treatment option for managing COVID-19 limited in low to middle income countries. The feasibility and economical sustainability of mAbs against SARS-CoV-2 seem to be optimal in localized epidemics or small outbreaks.[15]

REFERENCES

1. Wise J. COVID-19: WHO declares end of global health emergency. BMJ. 2023;381:1041. doi: https://doi.org/10.1136/bmj.p1041.
2. Paludan SR, Mogensen TH. Innate immunological pathways in COVID-19 pathogenesis. Sci Immunol. 2022;7(67):eabm5505. doi: 10.1126/sciimmunol.abm5505. Epub 2022 Jan 7.
3. Lamers MM, Haagmans BL. SARS-CoV-2 pathogenesis. Nat Rev Microbiol. 2022;20(5):270-84. doi: 10.1038/s41579-022-00713-0. Epub 2022 Mar 30.
4. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. [online]. 2023 [Accessed 3 October 2023]. Available from: https://covid19.who.int/
5. Yi J, Miao J, Zuo Q, et al. COVID-19 pandemic: A multidisciplinary perspective on the pathogenesis of a novel coronavirus from infection, immunity and pathological responses. Front Immunol. 2022;13:978619. doi: 10.3389/fimmu.2022.978619. eCollection 2022.
6. Zhou T, Su TT, Mudianto T, Wang J. Immune asynchrony in COVID-19 pathogenesis and potential immunotherapies. J Exp Med. 2020;217(10):e20200674. doi: 10.1084/jem.20200674.
7. Aleem A, Vaqar S. Monoclonal antibody therapy for high risk coronavirus (COVID 19) patients with mild to moderate disease presentations. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023
8. Wafa IA, Pratama NR, Budi DS, Sutanto H, Rosyid AN, Wungu CDK. The efficacy and safety of monoclonal antibody treatments against COVID-19: A systematic review and meta-analysis of randomized clinical trials. Acta Med Indones-Indones J Intern Med. 2023;55(3):243-54.
9. Chary M, Barbuto AF, Izadmehr S, Tarsillo M, Fleischer E, Burns MM. COVID-19 therapeutics: use, mechanism of action, and toxicity (vaccines, monoclonal antibodies, and immunotherapeutics). J Med Toxicol. 2023;19(2):205-18. doi: 10.1007/s13181-023-00931-9. Epub 2023 Mar 2.
10. Xu C, Rafique A, Potocky T, et al. Differential binding of sarilumab and tocilizumab to IL-6Rα and effects of receptor occupancy on clinical parameters. J Clin Pharmacol. 2021;61(5):714-24. doi: 10.1002/jcph.1795. Epub 2021 Jan 26.
11. Nhean S, Varela ME, Nguyen YN, et al. COVID-19: a review of potential treatments (corticosteroids, remdesivir, tocilizumab, bamlanivimab/etesevimab, and casirivimab/imdevimab) and pharmacological considerations. J Pharm Pract. 2023;36(2):407-17. doi: 10.1177/08971900211048139. Epub 2021 Oct 1.
12. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Clin Infect Dis. 2022:ciac724. doi: 10.1093/cid/ciac724. Online ahead of print.
13. Singh DD, Sharma A, Lee HJ, Yadav DK. SARS-CoV-2: Recent variants and clinical efficacy of antibody-based therapy. Front Cell Infect Microbiol. 2022;12:839170. doi: 10.3389/fcimb.2022.839170. eCollection 2022.
14. Park S, Je NK, Kim DW, Park M, Heo J. Effectiveness and safety of Regdanvimab in patients with mild-to-moderate COVID-19: a retrospective cohort study. J Korean Med Sci. 2022;37(13):e102. doi: 10.3346/jkms.2022.37.e102.
15. Focosi D, McConnell S, Casadevall A, Cappello E, Valdiserra G, Tuccori M. Monoclonal antibody therapies against SARS-CoV-2. Lancet Infect Dis. 2022;22(11):e311-26. doi: 10.1016/S1473-3099(22)00311-5. Epub 2022 Jul 5.
16. Burhan E, Susanto AD, Isbaniah F, et al. Pedoman tata laksana COVID-19. 4th ed [online]. Jakarta: Perhimpunan Dokter Paru Indonesia (PDPI) Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI) Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia (PAPDI) Perhimpunan Dokter Anestesiologi dan Terapi Intensif Indonesia (PERDATIN) Ikatan Dokter Anak Indonesia (IDAI); 2022 [Accessed 5 October 2023]. Available from: https://covid19.go.id/storage/app/media/Protokol/2022/Februari/Buku%20Tatalaksana%20COVID-19%205%20OP%20Edisi%204%20Jan%202022.pdf
17. Kim SB, Kim J, Huh K, et al. Korean Society of Infectious Diseases/National Evidence-based Healthcare Collaborating Agency recommendations for anti-SARS-CoV-2 monoclonal antibody treatment of patients with COVID-19. Infect Chemother. 2021;53(2):395-403. doi: 10.3947/ic.2021.0304.