Current Topics in Pharmacology
Vol. 25, 2021

Mini-Review

A brief overview about the latest news on SARS-CoV-2 therapeutic management

G. Calcaterra[1] and P. P. Bassareo[2,*]

[1]Postgraduate Medical School, University of Palermo, Italy. [2]University College of Dublin, Mater Misericordiae University Hospital and Our Lady's Children's Hospital Crumlin, Dublin, Ireland.

ABSTRACT

Loads of medications and vaccines are under investigation to prevent and heal coronavirus disease 2019 (COVID-19), which is putting a strain on healthcare systems worldwide. Among them, therapy with neutralizing monoclonal antibodies (nAbs) seems to be very promising in halting the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for the illness and in providing the patients with passive immunity. NAbs are designed to mimic the body's natural immune response. Coronavirus infection is mediated by the interplay between the viral spike and the tissue angiotensin-converting enzyme 2 (ACE 2) receptor found on the apical surface of numerous cell types. However, nAbs are capable of blocking this interaction. They bind to the spike protein, thus impeding SARS-CoV-2 to enter human cells and tagging it for destruction. NAbs can be crucial in preventing COVID-19 from progressing to a severe form, and potentially are a prophylaxis option to subjects who have been exposed to SARS-CoV-2, while still waiting to get a vaccine. This mini review provides the readers with an overview about what is already known and what is new about the use of these agents.

KEYWORDS: COVID-19, SARS-CoV-2, neutralizing monoclonal antibodies, spike protein, ACE 2.

*Corresponding author: piercard@inwind.it

INTRODUCTION

Loads of medications and vaccines are under investigation to prevent and heal coronavirus disease 2019 (COVID-19), which is putting a strain on healthcare systems worldwide [1, 2]. Among them, therapy with neutralizing monoclonal antibodies (nAbs) seems to be very promising in neutralizing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for the illness and providing patients with passive immunity [3]. nAbs are designed to mimic the body's natural immune response. Their mechanism of action is pretty much the same as that of human antibodies which are released by type B lymphocytes. nAbs are able to recognize and bind to specific antigens in a highly selective way. This triggers an appropriate immune system reaction against the virus. nAbs can be crucial in preventing COVID-19 from progressing to a severe form, and potentially are a prophylaxis option to subjects who have been exposed to SARS-CoV-2, while they are still waiting to get a vaccine [4]. This mini review provides the readers with an overview about what is already known and what is new about the use of these agents.

Neutralizing monoclonal antibodies: mechanism of action

The main target of SARS-CoV-2 nAbs is the surface spike glycoprotein that enables SARS-CoV-2 entering host cells. The binding site in the SARS-CoV-2 spike is found in the S1 C-terminal domain [5]. Essentially all nAbs have this protein as a target [6]. Coronavirus infection is mediated

by the interplay between the viral spike and the tissue angiotensin-converting enzyme 2 (ACE 2) receptor found on the apical surface of numerous cell types, those in the heart, testis, kidneys, gastrointestinal tract, and lungs the most [7]. On the contrary, ACE 2 is less expressed in other organs and tissues, for example the liver and placenta [8]. The infection may cause a downregulation of the enzyme and in turn a surge in Angiotensin II activity, thus triggering inflammation, release of pro-inflammatory cytokines like IL-6, and a pro-coagulant state with the possible onset of acute respiratory disease syndrome, also known as ARDS, myocarditis, exacerbation of acute coronary syndrome, disseminated intravascular coagulation, and generalized clot formation [7, 9]. However, nAbs are capable of blocking this interaction. They bind to the spike protein, thus impeding SARS-CoV-2 to enter human cells and tagging it for destruction [10]. Even though current knowledge about the molecular structure of the SARS-CoV-2 spike protein is growing, prior studies about other human coronaviruses (SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV)) have certainly facilitated this process [11]. The majority of nAbs identified to date specifically target the receptor-binding domain on the spike protein which enables SARS-CoV-2 to bind to the ACE 2 receptor [12, 13]. However, on the basis of the current knowledge of SARS-CoV and MERS-CoV, nAbs are likely to target other regions of the spike protein as well [14]. nAbs are usually produced by using laboratory techniques such as enzyme linked immunosorbent assay (ELISA) and flow cytometry assay (FCA) [15].

Neutralizing monoclonal antibodies: clinical application

Although about a hundred nAbs have been licensed for use by the American Food and Drug Administration now, only 3 of them are used to treat or prevent several infectious diseases, namely those induced by respiratory syncytial virus, anthrax, and *Clostridioides difficile*. Furthermore, two different nAbs proved to be effective in dropping Ebola viral infection-related mortality, if used during the early stages of the illness the most. One was made up of a combination of 3 nAbs, while the other was a single monoclonal antibody. The successful outcome against a life-threatening virus supports the potential administration of nAbs for coping COVID-19 [16].

Many nAbs have been or are on the way to be enrolled in clinical trials against SARS-CoV-2 sustained infection, with different degrees of symptoms, with the aim of blocking the disease progression. Taking into account the long half-life of the vast majority of nAbs (for example, around 3 weeks for IgG1), a single IgG infusion is likely to be enough. A potential limitation of nAbs administered against COVID-19 is their unpredictable bioavailability in tissues affected by the disease, especially the lungs, which are often the main target of SARS-CoV-2 infection [17]. Another still unanswered question is the potential onset of viral mutations which are resistant to nAbs treatment as time goes by. Accordingly, nAbs have been chosen to target the regions of the viral spike protein which are usually not involved in viral mutations. Other products include a combination of 2 nAbs targeting different sites on the spike protein.

Currently, there are 3 nAbs preparations with neutralizing activity against SARS-CoV-2 which got an emergency use authorization (EUA) to be administered for the treatment of COVID-19: bamlanivimab, bamlanivimab plus etesevimab, and casirivimab plus imdevimab (see Table 1).

The ideal patient for nAbs-based treatment has a mild-to-moderate COVID-19, is not hospitalized and does not require oxygen therapy, but is at high risk of degenerating to severe COVID-19, need for hospitalization, or both [4].

The EUA for bamlanivimab monotherapy and bamlanivimav plus etesevimab combination is mainly based on the outcomes from the BLAZE-1 trial. The latter is a randomized trial involving 49 US centres and more than six hundred non-hospitalized patients who tested positive for SARS-CoV-2 infection and had mild-to-moderate symptoms. Patients who received bamlanivimab monotherapy or placebo were enrolled first (June 17th-August 21st, 2020) and followed by subjects who got bamlanivimab and etesevimab or placebo (August 22nd-September 3rd, 2020). Among the enrolled patients, treatment with bamlanivimab and etesevimab, compared to placebo, was related with a statistically significant decrease in SARS-CoV-2

Table 1. Main neutralizing monoclonal antibodies.

Name	Code name	EUA date of release	Human trials
Bamlanivimab	LY-CoV555	November 2020	Blaze-1, Blaze-2, Active-2, Active-3 (stopped)
Etesivimab	LY3832479, LY-CoV016	February 2021	Blaze-1, Blaze-2, Active-2, Active-3 (stopped)
Casirivimab/imdevimab	REGN10933/REGN10987	November 2020	Recovery

viral load at day 11. No significant difference in viral load was observed for bamlanivimab monotherapy vs placebo. However, bamlanivimab monotherapy was associated with a reduction in the hospitalization rate at day 29 after treatment [18].

Of note, nAbs, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when given to hospitalized COVID-19 patients requiring high flow oxygen or intubation/mechanical ventilation. It means that they should be administered just to patient with symptoms from mild to moderate [4].

Other scientific evidence supporting the use of bamlanivimab came out of the preliminary results of the BLAZE-2 trial. It is a randomized, double-blind, placebo controlled trial to evaluate bamlanivimab in the nursing home setting. At week 8 after treatment, bamlanivimab significantly reduced the rate of symptomatic COVID-19 vs placebo in nursing home residents and in the overall nursing home population, staff included. No concerns as to safety were released, and the number of COVID-19 attributed resident deaths, although small, was all in the placebo group [19].

The EUA for casirivimab plus imdevimab is based on the results from the REG-COV2 trial, which suggest that the nAbs cocktail significantly reduced viral load and need for additional medical examination in outpatients with mild-to-moderate COVID-19, when compared to adding placebo to standard-of-care [20].

Other nABs are under study as to their potential role against SARS-CoV-2 [21].

Generally speaking, some patients taking nAbs may suffer from either an allergic or nonallergic i.v. infusion-related reaction. Both reactions are triggered by the activation of the immune system in response to the nAbs but occur in different ways. Infusion-related reactions are rare but can cause flushing, itching, shortness of breath, or hypotension. There are also potential side effects in receiving any i.v. medication, including pain, soreness, or bruising around the injection site [22].

CONCLUSIONS

To summarize, nAbs are progressively gaining an important new role in the management of many viral infections, including that caused by SARS-CoV-2. The first findings of the clinical trials which have been recently set up in the meantime seem to be very promising in terms of limiting or modifying COVID-19 course. A new therapeutic tool is on the horizon. Establishing the therapeutic or prophylactic efficacy of nAbs would be a major advance in the control of the COVID-19 pandemic.

CONFLICT OF INTEREST STATEMENT

Nothing to declare.

REFERENCES

1. Bassareo, P. P., Melis, M. R., Marras, S. and Calcaterra, G. 2020, Postgrad. Med. J., 96, 633-638.
2. Calcaterra, G., Bassareo, P. P., Barillà, F., Sergi, D., Chiocchi, M., Romeo, F. and Mehta, J. L. 2021, Curr. Cardiol. Rev., 17, 74-77.
3. Jiang, S., Zhang, X., Yang, Y., Hotez, P. J. and Du, L. 2020, Nat. Biomed. Eng., 4, 1134-1139.
4. Malani, P. N. and Golub, R. M. 2021, J.A.M.A, 325, 644-645.
5. Ibrahim, I. M., Abdelmalek, D. H., Elshahat, M. E. and Elfiky, A. A. 2020, J. Infect., 80, 554-562.
6. Marston, H. D., Paules, C. I. and Fauci, A. S. 2018, N. Engl. J. Med., 378, 1469-1472.

7. Barillà, F., Bassareo, P. P., Calcaterra, G., Romeo, F. and Mehta, J. L. 2020, J. Cardiovasc. Med. (Hagerstown), 21, 630-633.
8. Mameli, S., Marcialis, M. A., Bassareo, P. P. and Fanos, V. 2021, Panminerva. Med., doi: 10.23736/S0031-0808.21.04239-7, Epub ahead of print.
9. Mehta, J. L., Calcaterra, G. and Bassareo, P. P. 2020, Clin. Cardiol., 43, 1362-1367.
10. Lloyd, E. C., Gandhi, T. N. and Petty, L. A. 2021, J.A.M.A, 325, 1015.
11. Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C. L., Abiona, O., Graham, B. S. and McLellan, J. S. 2020, Science, 367, 1260-1263.
12. Ju, B., Zhang, Q., Ge, J., Wang, R., Sun, J., Ge, X., Yu, J., Shan, S., Zhou, B., Song, S., Tang, X., Yu, J., Lan, Yuan, J., Wang, H., Zhao, J., Zhang, S., Wang, Y., Shi, X., Liu, L., Zhao, J., Wang, X., Zhang, Z. and Zhang, L. 2020, Nature, 584, 115-119.
13. Pinto, D., Park, Y. J., Beltramello, M., Walls, A. C., Tortorici, M. A., Bianchi, S., Jaconi, S., Culap, K., Zatta, F., De Marco, A., Peter, A., Guarino, B., Spreafico, R., Cameroni, E., Case, J. B., Chen, R. E., Havenar-Daughton, C., Snell, G., Telenti, A., Virgin, H. W., Lanzavecchia, A., Diamond, M. S., Fink, K., Veesler, D. and Corti, D. 2020, Nature, 583, 290-295.
14. Taylor, P. C., Adams, A. C., Hufford, M. M., de la Torre, I., Winthrop, K. and Gottlieb, R. L. 2021, Nat. Rev. Immunol. doi: 10.1038/s41577-021-00542-x. Epub ahead of print.
15. Wan, J., Xing, S., Ding, L., Wang, Y., Gu, C., Wu, Y., Rong, B., Li, C., Wang, S., Chen, K., He, C., Zhu, D., Yuan, S., Qiu, C., Zhao, C., Nie, L., Gao, Z., Jiao, J., Zhang, X., Wang, X., Ying, T., Wang, H., Xie, Y., Lu, Y., Xu, J. and Lan, F. 2020, Cell. Rep., 32, 107918.
16. Marston, H. D., Paules, C. I. and Fauci, A. S. 2018, N. Engl. J. Med., 378, 1469-1472.
17. Jaworski, J. P. 2020, Biomed. J., S2319-4170(20)30209-2.
18. Gottlieb, R. L., Nirula, A., Chen, P., Boscia, J., Heller, B., Morris, J., Huhn, G., Cardona, J., Mocherla, B., Stosor, V., Shawa, I., Kumar, P., Adams, A. C., Van Naarden, J., Custer, K. L., Durante, M., Oakley, G., Schade, A. E., Holzer, T. R., Ebert, P. J., Higgs, R. E., Kallewaard, N. L., Sabo, J., Patel, D. R., Klekotka, P., Shen, L. and Skovronsky, D. M. 2021, J.A.M.A, 325, 632-644.
19. https://www.sciencemediacentre.org/expert reaction to press release from Lilly about their neutralising antibody bamlanivimab and results from the BLAZE-2 trial looking at prevention of COVID-19 in nursing homes in the US | Science Media Centre. Accessed on April 5th, 2021
20. https://investor.regeneron.com/news-releases/news-release-details/ Regeneron's REGN-COV2 Antibody Cocktail Reduced Viral Levels and Improved Symptoms in Non-Hospitalized COVID-19 Patients | Regeneron Pharmaceuticals Inc. Accessed on April 5th, 2021
21. Tuccori, M., Ferraro, S., Convertino, I., Cappello, E., Valdiserra, G., Blandizzi, C., Maggi, F. and Focosi, D. 2020, M.A.b.s, 12, 1854149.
22. Lloyd, E. C., Gandhi, T. N. and Petty, L. A. 2021, J.A.M.A, 325,1015.