SUNTEXT REVIEWS

SunText Review of Virology
ISSN: 2766-5003

Open Access
Case Report
Volume 2:1

Combination Therapy and Monoclonal Antibodies: The First Major Therapeutic Opportunity to Change the Clinical History in the Sars-Cov-2 Era: A Mini Review

Weimer LE[1,*], Cattari G[2], Binelli A[1], Fanales-Belasio E[3], Piras S[2] and Sensi F[4]

[1]National Center for Global Health, Istituto Superiore di Sanita, Rome, Italy
[2]Reparto COVID, Ospedale Marino-Alghero, ASSL Sassari, ATS Sardegna, Italy
[3]Department of Infectious Diseases, DMI, Istituto Superiore di Sanità, Rome, Italy
[4]Direzione ASSL Sassari, ATS Sardegna, Italy

[*]**Corresponding author:** Weimer LE, National Center for Global Health, Istituto Superiore di Sanita, Rome, Italy; E-mail: lilianaelenaweimer@gmail.com

Received date: 08 July 2021; **Accepted date:** 12 July 2021; **Published date:** 17 July 2021

Citation Weimer LE, Cattari G, Binelli A, Fanales-Belasio E, Piras S, Sensi F (2021). Combination Therapy and Monoclonal Antibodies: The First Major Therapeutic Opportunity to Change the Clinical History in the Sars-Cov-2 Era: A Mini Review. A Novel Case Report. SunText Rev Virol 2(1): 117.

DOI: https://doi.org/10.51737/2766-5003.2021.017

Abstract

In December 2019, the sudden arrival and devastating spread of the SARS-COV-2 pandemic has stimulated an accelerated programme of international research to identify effective ways to limit the spread of infection and to reduce the morbidity and mortality associated with SARS-COV-2 the novel coronavirus disease-19 (COVID-19). The SARS-CoV-2 pandemic has already infected more than 141 million people worldwide and resulted in 3.01 million deaths. Due to the limited number of vaccine for the general population in most countries, the combination of monoclonal antibody (mAb) remains an important Therapeutic Opportunity to change the Clinical History in the Sars-Cov-2 Era and the multiorgan involviment, especially in the elderly individuals. More than 50 monoclonal antibody-related clinical trials are being conducted in different countries around the world, with few of them nearing the completion of the third and fourth phase clinical trial. Recently the FDA (Food AND Drug Administration) approved the emergence use authorization of combination therapy of monoclonal antibody including REGEN-COV (casirivimab and imdevimab, administered together), the combination bamlanivimab - etesevimab and revoked the authorization (EUA) that allowed bamlanivimab therapy alone. This minireview explain the importance of Combination Therapy with Monoclonal Antibodies as The First Major Therapeutic Opportunity to change the Clinical History in the Sars-Cov-2 Era.

Keywords: Sars-Cov-2; Bamlanivimab - etesevimab

Background

In December 2019, the sudden arrival and devastating spread of the SARS-COV-2 pandemic has stimulated an accelerated programme of international research to identify effective ways to limit the spread of infection and to reduce the morbidity and mortality associated with SARS-COV-2 the novel coronavirus disease-19 (COVID-19) [1]. The SARS-CoV-2 pandemic has already infected more than 201 million people worldwide and resulted in 4,27 million deaths [2]. Due to the limited number of vaccine for the general population in most countries, the combination of monoclonal antibody (mAb) remains an important Therapeutic Opportunity to change the Clinical History in the Sars-Cov-2 Era and the multiorgan involviment, especially in the elderly individuals. More than 50 monoclonal antibody-related clinical trials are being conducted in different countries around the world, with few of them nearing the completion of the third and fourth phase clinical trial. Recently the FDA (Food AND Drug Administration) approved the emergence use authorization of combination therapy of monoclonal antibody including REGEN-COV (casirivimab and imdevimab, administered

together), the combination bamlanivimab - etesevimab and revoked the authorization (EUA) that allowed bamlanivimab therapy alone. This minireview explain the importance of Combination Therapy with Monoclonal Antibodies as The First Major Therapeutic Opportunity to change the Clinical History in the Sars-Cov-2 Era.

Combination with Monoclonal Antibodies in Sars-Cov-2 persons as Cocktail with Antiretroviral Drugs in HIV Infection

The mAbs are likely to aid in reducing viral load by interfering with virus entry into a cell by binding to viral spikes and thus inhibiting virus attachment to cell surface receptors or by targeting host cell receptors or co-receptors, thereby making the binding sites of host cells unavailable for SARS-CoV-2. Actually Bamlanivimab - etesevimab and casirivimab - imdevimab decrease viral load when given early on in the course of SARS-CoV-2 infection and favourably impact clinical outcomes for patients with mild-to-moderate COVID-19. Although full clinical trial data are pending, top-line and interim results from multiple trials suggest that the therapies may also function as prophylaxis in at-risk patients recently exposed to SARS-CoV-2. One signal emerging from early data is that patients with persistently higher viral load progress more frequently and this effect is most pronounced for patients with pre-existing risk factors for disease progression [3]. The cocktail therapy comprising casirivimab and imdevimab (REGN-COV2), block virus binding to the human ACE2 receptor, has been developed by Regeneron Pharmaceuticals and approved for EUA by the FDA on November 21, 2020. The recommended dose is 1200 mg for both mAbs as a single intravenous infusion dose for the treatment of adults and pediatric patients suffering from mild to moderate COVID-19, as well as those who are at high risk of progressing to severe COVID-19. But patients who are hospitalized due to COVID-19 or who require oxygen therapy due to COVID-19 or any other underlying non-COVID-19 related comorbidity were excluded from receiving the cocktail therapy as study findings demonstrated limited benefits of the drug in patients suffering from severe diseases. The authorization is based on positive phase-2 data announced in September and October from 799 adults in an ongoing randomized, double-blind, placebo-controlled trial of non-hospitalized patients ("outpatients") with COVID-19, in which significant reductions were observed in the level of the virus along with significantly fewer medical visits within 28 days of receiving the combination treatment . On further analysis, interim results from phase 1–2 trials in 275 patients published in December corroborated previous findings and demonstrated improved results in patients in whom endogenous immune response had not been initiated and patients who had high viral load at the start of mAb therapy [4]. The absence of co-morbidities does not completely eliminate the risk of severe disease and sequalae, and there is an urgent need for additional insight into a more personalized predictive algorithm to unlock as-yet-unidentified risk factors. The way to classify candidate patients for neutralizing mAbs would be to select patients who are expected to have poor antiviral responses (for example, elderly or immune compromised patients) or to identify patients with poor T cell and/or B cell function via experimental techniques (such as by serology or flow cytometry). Regarding the latter, there is a lack of published evidence on humoral immune response dynamics and correlation with clinical outcomes. Finally, antiviral and antimicrobial therapies are traditionally plagued by their promoting escape variants, and sometimes combination therapy can mitigate this risk. As a first-generation approach for neutralizing mAbs, monotherapies have been developed and have been demonstrated to be efficacious, but it is expected that a greater number of combination therapies will follow. For example, in phase II/III trials involving patients with COVID-19, bamlanivimab and the bamlanivimab and etesevimab combination had similarly improved magnitudes and timings of symptom relief relative to the placebo25. However, to date, the bamlanivimab and etesevimab combination does not appear to lead to the emergence of drug-resistant variants of SARS-CoV-2. This is similar to what has been observed for the other authorized neutralizing mAb combination (casirivimab and imdevimab), as already described herein [5].

Benefits of Monoclonal Antibodies Therapy: Does their use as a prophylactic or treatment potentially affect natural long-term immunity?

Considering the large doses used and the relative half-life of antibodies (~3 weeks for IgG molecules), there is a pertinent consideration whether the presence of circulating neutralizing mAbs could impact active immunity, whether through memory from infection or vaccination. From the collective clinical data with MAb114, REGN-EB3 and palivizumab, the general benefits and risks associated with neutralizing mAbs are similar to those observed with traditional passive immunization against infectious agents. The agents themselves are relatively tolerable for patients, efficacious during the early onset of disease symptoms and in certain cases as a prophylactic, but with limited efficacy once infections are severe. The distinctions between these therapies are largely logistical; CPT is more rapidly implemented during an emerging pandemic when few therapeutic options are yet available, while neutralizing mAbs take time to discover and it takes time for regulatory approval for their use to be obtained as well as to scale up manufacturing capacity. The use and promise of passive immunization during the coronavirus outbreaks of the

twenty-first century (that is, with SARS-CoV, Middle East respiratory syndrome-related coronavirus and SARS-CoV-2) have re-emphasized these past lessons while also highlighting additional insights, as we discuss next [6]. Fortunately today, the process to mass-produce recombinant mAbs has become scalable to meet demand and is cost-competitive with other treatments. Neutralizing mAbs overcome limitations intrinsic (for example, the risk of blood-borne diseases, time to development of detectable high-affinity antibodies and risk of low antibody titres, as well as variable epitope specificity. Furthermore, a high titre of neutralizing antibodies — which current evidence indicates is necessary for the efficacy-is inherent with neutralizing mAbs. As of April 2021, at least 20 neutralizing mAb therapies were being tested in late-stage clinical trials or had already been approved for use in nine infectious diseases, including RSV infection and Ebola.

HIV and COVID-19 as Twin's Pandemics, The Viral Variants and the Limit to the Effectiveness of the Therapies

The polyclonal nature of Convalescent Plasma Therapy, in which a spectrum of differentiated antibodies target multiple epitopes of the pathogen, may help to reduce this risk. Nevertheless, emerging preclinical data suggest SARS-CoV-2 spike (S) protein mutations escape from polyclonal serum and convalescent plasma has reduced neutralizing activity against some viral variants [7]. For mAbs, however, depending on the infectious agent and the epitope targeted, combinations of mAbs may be necessary to maintain efficacy and prevent treatment failure. Experience with mAbs targeting human immunodeficiency virus (HIV), which has a very high mutation rate, suggests that it may be more effective and durable to use multiple neutralizing antibodies (that is, combinational mAb therapy) rather than a single one [8]. These particular mAbs to HIV also need to be broadly neutralizing and target epitopes generally conserved among viral variants.

REGN-COV2 Therapy as the HAART Therapy in the HIV Era

REGN-COV2 is a combination of two potent neutralizing mAbs — namely, casirivimab and imdevimab, which are IgG1 mAbs with unmodified Fc regions. These two mAbs were chosen from a pool of more than 200 neutralizing mAbs present in the initial isolation of thousands of antibodies and were derived from parallel efforts using humanized mice and the sera of patients recovering from COVID-19 [9]. An ongoing phase I/II/III placebo-controlled trial (NCT04425629) is investigating the safety and efficacy of a single infusion of casirivimab and imdevimab — 2,400 mg (n = 266, interim), 8,000 mg (n = 267, interim) or matching placebo (n = 266)-for symptomatic adults who have not previously been hospitalized within 3 days of a positive active SARS-COV-2 diagnosis (and within 7 days of the first symptoms) 3. In the modified full analysis set for the phase I/II analysis, the median age was 42 years (7% aged 65 years or older), 85% of patients were white, 9% were Black and 34% were considered at high risk (for example, they were elderly, had obesity or had underlying chronic medical conditions). Pooled treatment achieved the primary end point of time-weighted average change from the baseline in viral load (log10 copies per millilitre), collected from a nasopharyngeal swab, in patients with a positive baseline for viral RNA (n = 665). The difference in time-weighted average from day 1 through day 7 for the pooled doses of casirivimab and imdevimab compared with placebo was −0.36 log10 copies per millilitre ($P < 0.0001$). The combination was reported to reduce viral load particularly in patients with higher viral loads who were seronegative at the baseline. On a key clinical end point, a lower proportion of patients treated with casirivimab and imdevimab had COVID-19-related medically attended visits (2.8% for pooled doses versus 6.5% for placebo). In post hoc analyses, a lower proportion of patients treated with casirivimab and imdevimab had COVID-19-related hospitalizations or emergency department visits compared with patients who received placebo (2% versus 4%). The absolute risk reduction for casirivimab and imdevimab compared with placebo was greater for patients at high risk of progression to severe COVID-19 and/or hospitalization (3% versus 9%). Collectively, these results supported the EUA of Regeneron's casirivimab and imdevimab cocktail in the United States in November 2020.

Bamlanivimab and Etesevimab Therapy

The BLAZE-1 trial studied bamlanivimab together with etesevimab (an S protein-binding IgG1 with a modified Fc region, resulting in null effector function) 25,72. Bamlanivimab and etesevimab together significantly decreased viral load (mean changes from the baseline and percentage of patients with persistent high viral load) compared with placebo at day 3 to day 11. Bamlanivimab- and etesevimab-treated patients had fewer COVID-19-related hospitalizations relative to the placebo group (5.8% for placebo reduced to 0.9% for bamlanivimab together with etesevimab). Recently released placebo-controlled phase III data from 1,035 patients randomized 1:1 to receive bamlanivimab together with etesevimab versus placebo demonstrated that in high-risk ambulatory patients (including patients aged 12–17 years with specific risk factors and patients aged 18 years or older with specific adult risk factors) treatment with bamlanivimab and etesevimab together was associated with a 70% reduction in COVID-19-related hospitalizations and deaths relative to placebo treatment (7.0% for placebo reduced to 2.1% for bamlanivimab together with etesevimab) [10]. On the basis of these data, an

additional EUA of bamlanivimab together with etesevimab has been issued.

Monoclonal Antibodies Therapies in Severe COVID-19

There are concurrent studies investigating neutralizing mAbs for patients hospitalized with severe COVID-19. The REGN-COV2 trial in hospitalized patients enrols patients with or without supplemental oxygen and is ongoing. In prospectively designed analysis of REGN-COV2, there may be clinical benefit in patients treated with casirivimab and imdevimab and who were seronegative at the time of treatment76. In the ACTIV-3 RCT (n = 326, 1:1 randomization), bamlanivimab added to standard of care (typically including remdesivir) did not demonstrate additional clinical benefit in hospitalized patients [11]. In line with similar studies investigating CPT or neutralizing mAbs for patients with severe viral disease (including COVID-19), the evidence indicates that rapid viral clearance, in itself, is insufficient. Rather, additional factors, such as an excessive immune response, are the primary drivers for continued disease in this particular patient population. Thus, early disease seen in outpatients is likely virally driven, whereas the pathophysiology for inpatient advanced disease is predominantly a postviral or periviral phenomenon, with clinical status uncoupled from viral load.

Adverse events associated with monoclonal antibody therapies

In terms of risk associated with mAb treatment of COVID-19, treatment-associated adverse events were comparable to those with placebo. The most frequent side effects observed in RCTs include nausea, diarrhoea, dizziness, headache and vomiting. One per cent of patients receiving casirivimab and imdevimab reported a grade 2 or higher infusion-related reaction within 4 days of administration (comparable to 1% reported for placebo treatment). In the phase II portion of BLAZE-1, nine patients reported an infusion-related reaction (1.9% (6/309) with bamlanivimab monotherapy, 1.8% (2/112) with bamlanivimab and etesevimab together, and 0.6% (1/156) with placebo). Most reactions occurred during infusion; these were mild in severity and were not dose related. Regarding evidence of ADE, in vitro data indicate neutralizing mAbs do not enhance productive infection of immune cells with SARS-CoV-2. From the clinical data available to date, there is no clear evidence these therapies result in enhanced immune responses consistent with ADE. Furthermore, the safety profiles of modified and modified plus unmodified mAbs to treat SARS-CoV-2 infection are similar, suggesting that ADE may not play a role in clinical outcomes.

Emergence of drug-resistant SARS-CoV-2 strains as Hiv Therapy

For patients with Sars-Cov-2 who receive neutralizing mAbs, there is potential for the development of drug-resistant variants as HIV Antiretroviral Therapy, which become more obvious when selective pressure is applied in the setting of drug treatment [12]. For bamlanivimab, non-clinical studies using serial passage of SARS-CoV-2 and directed evolution of the SARS-CoV-2 S protein identified viral variants (E484D/K/Q, F490S, Q493R and S494P, amino acid substitutions in the S protein RBD) that had increased resistance to this drug. In clinical trials of bamlanivimab, genotypic and phenotypic testing are monitoring SARS-CoV-2 strains for potential S protein variations that are associated with bamlanivimab resistance. In the BLAZE-1 RCT, which was limited to US investigative sites, known bamlanivimab-resistant variants at the baseline were observed at a frequency of 0.27% to date. In the same trial, treatment-emergent variants were detected at S protein amino acid positions E484, F490 and S494 (including E484A/D/G/K/Q/V, F490L/S/V and S494L/P); considering all variants at these positions, 9.2% and 6.1% of participants in the 700-mg bamlanivimab arm (the EUA dose) harboured such a variant after the baseline at allele fractions of 15% or greater and 50% or greater, respectively, compared with 8.2% and 4.1%, respectively, of participants in the placebo arm. Most of these variants were first detected on day 7 following infusion, and were detected at only a single time point. The clinical impact of these variants is currently unknown. As with bamlanivimab, casirivimab and imdevimab therapy has the potential to lead to the development of resistant viral variants. In non-clinical studies, serial passage of vesicular stomatitis virus (VSV) encoding the SARS-CoV-2 S protein in the presence of the drugs identified escape variants with reduced susceptibility to casirivimab (K417E/N/R, Y453F, L455F, E484K, F486V and Q493K) or imdevimab (K444N/Q/T and V445A). Each viral variant showing reduced susceptibility to one mAb remained susceptible to the other mAb; all identified variants retained susceptibility to the combination. In a separate experiment, neutralization assays were performed with VSV pseudotyped with 39 variants of the S protein identified in circulating SARS-CoV-2. The G476S, S494P and Q409E variants had reduced susceptibility (5-fold, 5-fold, and 4-fold, respectively) to casirivimab, and the N439K variant had reduced susceptibility (463-fold) to imdevimab. The casirivimab and imdevimab combination was active against all individual variants tested. It has been reported that the combination of mutants at residues 417 and 439 may abrogate the effectiveness of the casirivimab and imdevimab combination [13]. In the casirivimab and imdevimab RCT NCT04425629, interim data indicated only one variant (G446V) detected in 4.5% of participants at an allele fraction of 15% or greater. However, not all variants must be considered clinically relevant mutations associated with resistance to treatment. During the Ebola outbreak in 2018, a genomic

assessment of 48 viral genomes determined that this outbreak was due to a distinct viral variant. The sequence information allowed researchers to evaluate the relevance of the distinct mutations to the available vaccine and therapeutics and to conclude that the neutralizing antibodies MAb114 and ZMapp would likely be effective against the currently circulating variant. A similar practice for SARS-CoV-2 surveillance may be prudent to determine whether emergent S protein variants pose a threat to the efficacy of neutralizing mAb therapies. Indeed, three SARS-CoV-2 variants of particular interest have been identified and are circulating globally. In the United Kingdom, a variant called 'B.1.1.7' with a large number of mutations was identified in the autumn of 2020. In South Africa, a variant called 'B.1.351 was identified. Originally detected in early October 2020, B.1.351 shares some mutations with B.1.1.7. In Brazil, a variant called 'P.1' was identified that contains a set of additional mutations that may affect its ability to be recognized by first-generation neutralizing mAbs and by the immune responses generated by first-generation vaccines. Although these variants have been detected in the United States, according to real-time data accessed via the GISAID COVID-19 variant tracker82 these COVID-19 variants do not currently represent a significant proportion of COVID-19 infections in the United States, while recent California (B.1.427/B.1.429) and New York (B.1.526) variants do. To date, the effect of these variants on the neutralizing capacity of vaccines and mAbs is unknown. A recent preprint suggests that the variants identified in the United Kingdom and South Africa are more resistant to vaccine. Bamlanivimab and imdevimab maintain full neutralization activity against the primary SARS-CoV-2 receptor-binding site variants (69-70del and N501Y) implicated in the strain originating in the United Kingdom, suggesting that these mAbs should maintain full activity against the new strain originating in the United Kingdom. From what is known about the strains that were first identified in South Africa, Brazil as well as the ones in California and New York, it appears that some of the first generation of antibody therapies may not be as effective and it will be important for physicans to refer to the most up to date factsheet.

Conclusion

In conclusion, monoclonal antibodies are, and will most likely continue to be, important therapeutic options with potential utility in both prophylactic and treatment setting, going into the 21st century, not just for SARS-CoV-2 but also for other infectious pathogens too. Efforts should be directed towards developing monoclonal antibodies that are highly effective, can be developed by a fraction of a current cost, and for whom there is a specific beneficiary group.

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020; 395: 470-473.
2. Novel coronavirus. Situation report 191. Geneva. World Health Organization. 2020.
3. Chen P. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med. 2021; 384: 229-237.
4. DeFrancesco L. COVID-19 antibodies on trial. Nat Biotechnol. 2020; 38: 1242-1252
5. Taylor PC, Adams AC, Hufford MM. Neutralizing monoclonal antibodies for treatment of COVID-19. Nat Rev Immunol. 2021.
6. Pecetta S, Finco O, Seubert A. Quantum leap of monoclonal antibody (mAb) discovery and development in the COVID-19 era. Semin Immunol. 2020; 50.
7. Bar Y, Gruell H. Safety and antiviral activity of combination HIV-1 broadly neutralizing antibodies in viremic individuals. Nat Med. 2018; 24: 1701-1707.
8. Scheid JF. HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption. Nature. 2016; 535: 556-560.
9. Hansen J, Baum A, Pascal KE, Russo V, Giordono S, Wloga E, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Sci. 2020; 369: 1010-1014.
10. Gottlieb RL. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA. 2021; 325: 632-644.
11. Weinreich DM. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. N Engl J Med. 2020; 34: 238-251.
12. Greaney AJ. Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition. Cell Host Microbe. 2021; 29: 44-57.
13. Thomson EC, Rosen LE, Shepherd G, Filipe ADS, Davis C, piccoli L, et al. The circulating SARS-CoV-2 spike variant N439K maintains fitness while evading antibody-mediated immunity. Cell. 2021; 18: 1171-1187.

Citation: Weimer LE, Cattari G, Binelli A, Fanales-Belasio E, Piras S, Sensi F (2021). Combination Therapy and Monoclonal Antibodies: The First Major Therapeutic Opportunity to Change the Clinical History in the Sars-Cov-2 Era: A Mini Review. A Novel Case Report. SunText Rev Virol 2(1): 117.