

The populations that were treated in the PolyIran trial and TIPS-3 would be considered to be at intermediate risk, with an annual event rate in the control group of 1.8% and 1.3%, respectively. Given that a large proportion of total events of atherosclerotic cardiovascular disease occur in such populations, effective treatment strategies targeting such groups, in addition to targeting those with established disease, are likely to have major global public health effects.

Ischemic heart disease and atherosclerotic stroke are among the leading causes of health loss globally. Yet, health systems either have not been sufficiently responsive or are unprepared to deliver equitable, high-quality primary care in cardiovascular disease prevention and control.⁵ The findings of TIPS-3 support the inclusion of multidrug therapy for cardiovascular disease prevention in the World Health Organization “best buys” for noncommunicable disease prevention and control as the lone health-system approach that is potentially highly cost-effective.⁶ Other population-based strategies, including comprehensive tobacco regulation, food reformulation, and mass-media campaigns to promote healthy, sustainable eating and activity, still need to be implemented urgently to achieve global goals. However, patients with atherosclerotic cardiovascular disease and persons who are at risk for atherosclerotic cardiovascular disease can also derive health benefits from pharmacotherapy, and thus poly pill therapy represents the most scalable intervention to date, given the totality of data.

Implementation challenges still need to be

overcome at the regulatory, manufacturing, distribution, and clinical levels to ensure that a reliable supply of high-quality and affordable poly pills is available for eligible patients.⁷ At present, poly pills have limited availability around the world, including in the United States. These challenges deserve attention; the findings of TIPS-3 support a contention that poly pills will be central to any comprehensive strategy to improve global cardiovascular health.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago (M.D.H.); and the George Institute for Global Health, University of New South Wales, Sydney (M.D.H., A.P.).

1. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419.
2. Bahiru E, de Cates AN, Farr MR, et al. Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases. *Cochrane Database Syst Rev* 2017;3:CD009868.
3. Roshandel G, Khoshnia M, Poustchi H, et al. Effectiveness of poly pill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial. *Lancet* 2019;394:672-83.
4. Yusuf S, Joseph P, Dans A, et al. Poly pill with or without aspirin in persons without cardiovascular disease. *N Engl J Med* 2021;384:216-28.
5. GBD 2019 Viewpoint Collaborators. Five insights from the Global Burden of Disease Study 2019. *Lancet* 2020;396:1135-59.
6. Tackling NCDs: “best buys” and other recommended interventions for the prevention and control of noncommunicable diseases. Geneva: World Health Organization, 2017 (<https://apps.who.int/iris/handle/10665/259232>).
7. Huffman MD, Salam A, Patel A. Implementation strategies for cardiovascular poly pills. *JAMA* 2019 November 25 (Epub ahead of print).

DOI: 10.1056/NEJMe2033310

Copyright © 2021 Massachusetts Medical Society.

Monoclonal Antibodies to Disrupt Progression of Early Covid-19 Infection

Myron S. Cohen, M.D.

By the end of 2020, more than 19 million Americans had received the diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.¹ Although a substantial proportion of these infections remained asymptomatic, complications of coronavirus disease 2019 (Covid-19)

had led to more than 330,000 deaths in the United States.¹ During the past year, a remarkable effort has been devoted to the development of vaccines to prevent Covid-19 and to reduce morbidity and mortality among those who are infected. Equally important is the development

of treatments that can prevent the progression of Covid-19 from the inception of infection.

In this issue of the *Journal*, two groups of investigators report the findings of trials of such treatments involving patients with Covid-19. In the first trial, Weinreich et al.² report interim results of a trial of a combination of two monoclonal antibodies, casirivimab and imdevimab (together called REGN-COV2), which is directed against the spike protein of SARS-CoV-2³ for use in patients with early infection. The trial enrolled outpatients who had presented within 7 days after the onset of symptoms and within 72 hours after a positive result on quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing of nasopharyngeal swab samples. The patients were randomly assigned in a 1:1:1 ratio to receive a single intravenous infusion of either 2.4 g or 8 g of REGN-COV2 or placebo. Key end points were the change from baseline in viral load from day 1 through day 7 and the percentage of patients who had at least one Covid-19–related medically attended visit through day 29.

In the first 275 patients, those who received either dose of REGN-COV2 had lower SARS-CoV-2 RNA levels than those who received placebo. Patients who had not had an autologous antibody response at the time of randomization had a higher baseline nasopharyngeal RNA viral load and a steeper reduction in viral load after the administration of REGN-COV2 than those who were seropositive at randomization. A small number of patients (12) required a medically attended visit within the 29-day follow-up period, with a larger percentage in the placebo group.

These results complement the findings of a trial by Chen et al.,⁴ who evaluated three doses (700 mg, 2800 mg, and 7000 mg) of a single monoclonal antibody, bamlanivimab (LY-CoV555),⁵ which was administered to 452 outpatients who presented with Covid-19 a median of 4 days after symptom onset; 309 patients received bamlanivimab, and 143 received placebo. Reductions in nasopharyngeal RNA levels of SARS-CoV-2 were detected after 3 days of treatment in all groups, with a greater decline in the combined-dose bamlanivimab group than in the placebo group. Through day 29, hospitalization was reported in 14 patients: 5 (1.6%) in the bamlanivimab group and 9 (6.3%) in the placebo group. Bamlanivimab was associated with a greater reduction in

symptoms of Covid-19 than was placebo. In a continuation of this clinical trial, patients are now receiving a combination of bamlanivimab and etesevimab (LY3832479) to overcome or prevent antibody resistance (ClinicalTrials.gov number, NCT04427501).

These studies used the measurement of SARS-CoV-2 with RT-PCR as a surrogate for the magnitude of viral infection and perhaps viral replication.⁶ The results suggest that monoclonal antibodies serve as an antiviral agent to reduce the viral load in the nasopharynx. The effects of monoclonal antibodies and other drugs on viral load may prove to be an important criterion for the development of agents to treat early Covid-19. In the trial by Chen et al., patients with persistently high nasopharyngeal RNA shedding on day 7 were more likely to be hospitalized than those with lower levels (12% vs. 0.9%). This finding suggests that persistent SARS-CoV-2 replication in the nasopharynx portends progression of Covid-19, which may be limited by early antibody treatment or by a rapid autologous immune response.

The results reported by Weinreich and Chen and their colleagues provided key information for the Food and Drug Administration to consider in its decision regarding emergency use authorization for bamlanivimab⁷ and the casirivimab–imdevimab combination⁸ for adults and children over the age of 12 years who have mild or moderate Covid-19 and are at high risk for severe disease. No added benefit for these antibodies was shown in trials involving sicker hospitalized patients (NCT04426695 and NCT04342897), perhaps because in later stages of the disease, inflammation and coagulopathy play a greater role in the patient's outcome than viral replication.

Such monoclonal antibodies may also be successful in preventing SARS-CoV-2 infection⁹ as an alternative to vaccination for people who cannot take a vaccine or need more immediate prophylaxis either before or after exposure. Trials of such prophylaxis are ongoing in skilled nursing facilities (NCT04497987) and among household contacts of patients with SARS-CoV-2 infection (NCT04452318). Dozens of investigators and companies are working on additional antibodies, which include modifications designed to prolong the in vivo half-life of these drugs or to allow intramuscular or subcutaneous delivery.¹⁰

The findings from these two clinical trials are provocative and promising. Eli Lilly and Regeneron are greatly expanding their studies to better define the clinical benefits of their monoclonal antibodies, and Operation Warp Speed and the National Institutes of Health plan to compare several such antibodies for treatment in their ACTIV-2 trial involving outpatients with Covid-19 (NCT04518410). If these drugs prove to provide reliable early treatment of Covid-19, they will greatly improve the management of the infection. Such treatments are logistically challenging but should inspire early and rapid testing of persons at high risk for SARS-CoV-2 infection. Interventions that prevent the progression of Covid-19 can then be expected to reduce the morbidity and mortality of infection, the frequency of hospitalizations, and the current unbearable strain on the U.S. health care system.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the University of North Carolina Chapel Hill School of Medicine, Chapel Hill.

1. Johns Hopkins University. The Center for Systems Science and Engineering (CSSE) COVID-19 Dashboard (<https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6>).
2. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-

COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med* 2021;384:238-51.

3. Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science* 2020;369:1010-4.

4. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med* 2021;384:229-37.

5. Jones BE, Brown-Augsburger PL, Corbett KS, et al. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. October 1, 2020 (<https://www.biorxiv.org/content/10.1101/2020.09.30.318972v1>). preprint.

6. Cevik M, Tate M, Lloyd O, Maraolo A, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. July 29, 2020 (<https://www.medrxiv.org/content/10.1101/2020.07.25.20162107v2>). preprint.

7. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes monoclonal antibody for treatment of COVID-19. FDA news release, November 9, 2020 (<https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19>).

8. Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes monoclonal antibodies for treatment of COVID-19. FDA news release, November 21, 2020 (<https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19>).

9. Marovich M, Mascola JR, Cohen MS. Monoclonal antibodies for prevention and treatment of COVID-19. *JAMA* 2020;324:131-2.

10. Renn A, Fu Y, Hu X, Hall MD, Simeonov A. Fruitful neutralizing antibody pipeline brings hope to defeat SARS-Cov-2. *Trends Pharmacol Sci* 2020;41:815-29.

DOI: 10.1056/NEJMe2034495

Copyright © 2021 Massachusetts Medical Society.