Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COMMENTARY

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Updates for Health Providers on Monoclonal Antibodies for COVID-19: Less Promising Adjunct and Never an Alternative to Vaccinations

The United States rapidly became and remains to this date the epicenter of the COVID-19 pandemic, based on total cases and deaths. As of December 14, 2021, the United States has experienced over 50 million cases and 800,000 deaths. Healthcare providers should be aware that 119 days elapsed between the 600,000 and 700,000 death milestones but only 74 days elapsed between 700,000 and 800,000. In the United States, deaths have increased by 27.8% and averaged 1283 per day during the past week. In contrast, the capacity of a 747-400 jet is 416 people. Thus, each day, US deaths from COVID-19 exceed the deaths that would occur if three 747's filled to capacity crashed with no survivors. Further, the risks of death from COVID-19 are now higher among the US population than myocardial infarction, stroke, or cancer.[1]

Healthcare providers are considered by the general public of the United States to be their most reliable source of information about COVID-19.[2] In this commentary we provide to healthcare workers an update on monoclonal antibody treatment of early COVID-19. The reliable detection of small to moderate benefits, which can be clinically extremely worthwhile for common and serious diseases like COVID-19, requires large-scale randomized trials of sufficient size, dose, and duration.[3] There are 3 monoclonal antibody treatments that have been tested in large-scale randomized trials, namely bamlanivimab plus etesevimab (Lilly), sotrovimab (GlaxoSmithKline) as well as casirivimab and imdevimab, (Regeneron). We urge healthcare providers to be aware that these are promising agents in the early treatment of COVID-19 but should never be considered alternatives to vaccinations.

With respect to bamlanivimab plus etesevimab, the phase 2 results of the Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial led to the US Food and Drug Administration issuing an Emergency Use Authorization (EUA) for bamlanivimab plus etesevimab.[4] In phase 3 of the BLAZE-1 trial, 1035 outpatients aged 12 or over with mild or moderate COVID-19 at high risk for severe disease were assigned at random to the combination of bamlanivimab and etesevimab or placebo. There was a 2.1% rate of hospitalization or death among those assigned at random to the active drug, compared with 7.0% among those given placebo. Further, there were no deaths in the treated group and 10 in the placebo group, 9 of which were due to COVID-19.[5]

With regard to sotrovimab, among 583 non-hospitalized patients with symptomatic COVID-19 (≤5 days after the onset of symptoms) and at least 1 risk factor for disease progression, 291 were assigned to receive a single infusion of sotrovimab at a dose of 500 mg and 292 were given placebo. The primary efficacy outcome was hospitalization (for >24 hours) for any cause or death within 29 days after

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randomization. In a prespecified interim analysis, 3 patients (1%) in the sotrovimab group, compared with 21 patients (7%) in the placebo group, had disease progression leading to hospitalization or death (relative risk reduction, 85%; 97.24% confidence interval, 44 to 96; $P = .002$). There were no admissions to the intensive care unit or deaths in the treated group compared with 5 and 1, respectively, in the placebo group. There were no excesses of adverse or serious adverse events in the treated group. Thus, sotrovimab significantly reduced the risk of progression of COVID-19.

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) consists of a series of large-scale randomized trials testing various promising but unproven treatments for COVID-19. The trial first enrolled patients in the United Kingdom but since then have randomized eligible patients in Indonesia, Nepal, and Vietnam. To date, RECOVERY has tested 10 drugs. One of these is the monoclonal antibody treatment of casirivimab and imdevimab.[6]

Among 9785 patients, randomized to casirivimab 4 grams and imdevimab 4 grams or usual standard of care, 5272 (54%) were seropositive and 32% seronegative at baseline. For the patients who were seronegative at baseline because they had not mounted an antibody response, the rate of death at 28 days was significantly reduced by 20% among those who were assigned at random to the infusion of casirivimab and imdevimab. Further, the duration of hospital stay was about 4 days shorter among those assigned at random to the antibody combination. In all randomized subjects there was a possible but nonsignificant 6% reduction in deaths.

On August 10, 2021, the US Food and Drug Administration revised their EUA for casirivimab and imdevimab, administered together. The EUA was issued for the treatment and post-exposure prophylaxis. There are no randomized data for pre-exposure prophylaxis for prevention of COVID-19 or for use in patients who are hospitalized due to COVID-19 or require oxygen therapy, or for people currently using chronic oxygen therapy because of an underlying comorbidity who require an increase in baseline oxygen flow rate due to COVID-19.[7] Thus, healthcare providers should be aware that this treatment is approved for post-exposure prophylaxis in all individuals aged 12 years of age and older weighing at least 89.8 pounds (or 40 kilograms) who are at high risk for progression to severe COVID-19.[7]

Based on the randomized evidence in the context of supporting data from basic research and other descriptive and observational analytic research, healthcare providers should counsel their patients that monoclonal antibody treatment seems to be an effective and safe means to reduce hospitalization and death in the early treatment of COVID-19. Of course, they are only as good as their availability. Fortunately, technology is being developed to facilitate subcutaneous administration in the offices of health providers.[8]

The United Kingdom and South Africa are among the world leaders in genomic surveillance of COVID-19, whereas the United States is ranked 43rd.[9] Thus, it was not surprising that the omicron variant was first identified in South Africa and became the dominant variant in a few weeks. This variant is the latest but certainly will not be the last. The United States is likely to experience a similar pattern to that which is already occurring in the United Kingdom. On December 17, 2021, the UK Health Security Administration presented their latest data on 116,186 COVID-19 cases from November 15 to December 6, of which 115,407 were delta and 777 were omicron. The reinfection rates for omicron doubled in 2.5 days and were 5.4 times greater than delta's. The relative severity of omicron compared with delta remains unclear. Nonetheless, the increasing prevalence and increased transmissibility of omicron underscores the need for more vaccinations but also more therapies of early onset COVID-19.[10] Healthcare providers should emphasize to their patients that the use of monoclonal antibody treatment for early COVID-19 should always be considered to be only an adjunct and never an alternative to vaccinations to prevent COVID-19. Benjamin Franklin once said that "an ounce of prevention is worth a pound of cure." When addressing COVID-19 with patients, healthcare providers may wish to consider that an ounce of prevention with vaccinations is worth far more than a pound of treatment with monoclonal antibodies. Finally, on January 24, 2022, the US FDA withdrew the EUA for casirivimab and imdevimab as well as bamlanivimab and etesevimab based on the >99% prevalence of the omicron variant to which these two antibody treatments are ineffective.[11]

DEDICATION

We dedicate this manuscript to the memory of our mentor, colleague, and friend Donald B. Louria, MD (1928-2021).

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