Medical News & Perspectives

Monoclonal Antibodies for COVID-19 Preexposure Prophylaxis Can’t Come Fast Enough for Some People

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Retired family physician Brian Koffman, MD, constantly fields questions that begin with the same 6 words: When will I be able to...hug my grandchildren...eat in a restaurant...go to an art gallery?

The inquiries come from some of the estimated 200,000 people in the US who, like 70-year-old Koffman of Chula Vista, California, are living with chronic lymphocytic leukemia (CLL).

While their healthy, fully vaccinated peers have resumed enjoying activities that most took for granted before COVID-19, many with CLL or other factors that compromise the immune system such as medication to prevent organ rejection after transplant surgery continue to shelter in place more than a year and a half into the pandemic.

They’ve played by the rules, as Koffman puts it, completing their recommended course of 3 messenger RNA (mRNA) vaccines. But they can’t count on vaccination to protect them against SARS-CoV-2 because of their blunted immune response to the vaccines as well as to the virus.

Instead, they’re pinning their hopes on neutralizing monoclonal antibodies for an extra layer of protection that will free them from the confines of their homes.

Made in a laboratory, anti-SARS-CoV-2 monoclonal antibodies can be derived from the B cells of people who’ve recovered from COVID-19 or from humanized mice. They target epitopes on the SARS-CoV-2 spike protein. Infused or injected, monoclonal antibodies provide almost immediate, albeit temporary, "passive immunity" no matter the state of the recipient’s immune system.

The US Food and Drug Administration (FDA) already has authorized emergency use of anti-SARS-CoV-2 monoclonal antibodies to treat mild to moderate COVID-19 in patients at risk of developing more severe disease. More recently, the FDA also authorized emergency use of Regeneron’s monoclonal antibody cocktail casirivimab and imdevimab for postexposure prophylaxis—preventing illness in people at high risk of severe disease who’ve been exposed to someone with laboratory-confirmed SARS-CoV-2.

But what Koffman calls the "holy grail" of people with CLL is not yet available outside clinical trials: monoclonal antibodies for preexposure prophylaxis. That might soon change, though. In early October, AstraZeneca asked the FDA to grant Emergency Use Authorization (EUA) for both preexposure and postexposure prophylaxis for the company’s investigational monoclonal antibody combination of tixagevimab and cilgavimab, now called AZD7442.

"I get emails every day: What am I going to do? When can I get monoclonal antibodies?" said Myron Cohen, MD, director of the allergy, immunology, and transplantation division at the National Institute of Allergy and Infectious Diseases (NIAID) noted in an interview.

For example, in September, Regeneron announced that the US Department of Health and Human Services and the Department of Defense would buy 1.4 million additional doses of its monoclonal antibody cocktail (REGEN-COV), authorized for postexposure prophylaxis and treatment of mild to moderate COVID-19, at a cost of $2100 per dose. Regeneron’s product is typically administered by intravenous infusion but can be injected subcutaneously to speed treatment. In the UK, where Regeneron’s monoclonal antibody cocktail has received conditional marketing authorization for preexposure and postexposure prophylaxis and is sold as Ronapreve, people will need to get it every 4 weeks to maintain protection.

AstraZeneca would not provide an estimate of the per-dose cost of AZD7442 but...
said in a statement to JAMA that “We are committed to working with international and government agencies around the world to make AZD7442 accessible.”

In March, the company said a modified agreement with the federal government to provide up to 500,000 additional doses of AZD7442, contingent on FDA authorization, was worth $205 million (the US government has also bought hundreds of thousands of doses of Eli Lilly’s monoclonal antibodies bamlanivimab and etesevimab, authorized for use together to treat COVID-19). AZD7442, developed with support from the federal government, is given in 2 intramuscular injections (1 of each monoclonal antibody in the cocktail), and preliminary pharmacokinetic modeling, which has not been peer-reviewed, suggests protection could last up to 12 months.

“From NIAID's perspective, effective vaccination is our primary goal for prevention,” Rotrosen said. “If we can achieve it with boosters—it may not be just a third booster; some people might require a fourth booster—that’s better than monoclonal antibodies.”

Plus, while the casirivimab and imdevimab combination and AZD7442 appear to be effective against Delta and other SARS-CoV-2 variants, it’s not known whether future variants will be susceptible to them, he noted. In April, the FDA revoked the EUA for Lilly’s bamlanivimab as a solo COVID-19 treatment because of increased resistance to virus variants.

Who Needs It?

Numerous articles have noted that while only 3% of people are immunocompromised, they represent 40% of COVID-19 infections in fully vaccinated individuals.

Those estimates come from studies in 2 different countries. The 3% figure, rounded up from 2.7%, is derived from a 5-year-old research letter in JAMA that’s based on self-reported data from the 2013 National Health Interview Survey, which is conducted annually via household interviews. The survey asked people 10 questions about immunosuppression, such as, “Have you ever been told by a doctor or other health professional that your immune system is weakened?”

The 40% estimate comes from a small study of 152 fully vaccinated patients hospitalized with COVID-19 in Israel, where, unlike in the US, virtually everyone has received the BNT162b2 (Pfizer-BioNTech) COVID-19 mRNA vaccine. Common causes of immunosuppression in the study population included long-term corticosteroid treatment, chemotherapy, solid organ transplant, and anti-CD20 treatment, which includes the monoclonal antibody rituximab. Rituximab has become a cornerstone in the management of many cancers, including CLL, since the FDA licensed it in 1997.

Like other anti-CD20 therapies, rituximab targets an epitope on the surface of B cells, the white blood cells that generate antibodies. Even before COVID-19, rituximab was associated with decreased vaccine responses determined by protective antibody titers.

Cohen cautioned against lumping together everyone with a compromised immune system when determining who might need prophylactic monoclonal antibodies along with 3 doses of COVID-19 vaccine.

“We’re trying to understand the universe of people who are compromised,” he said in an interview. Cohen noted that Regeneron recently launched a trial to study its monoclonal antibody combination in nearly 9000 fully vaccinated volunteers aged 12 years or older with a compromised immune system due to a variety of conditions including cancer, multiple sclerosis, HIV, or immunosuppressant drugs.

Some people with compromised immune systems do mount an effective response to COVID-19 vaccines and wouldn’t need prophylactic antibody prophylaxis, Cohen said. “But if you’re vaccinated and you acquire COVID, we would still give you a monoclonal antibody,” he emphasized, adding that it’s unlikely the treatment would interfere with vaccine-induced immune responses. (However, given a lack of data about the safety and efficacy of vaccines in people who receive monoclonal antibodies to treat COVID-19, the CDC recommends that people who aren’t fully vaccinated defer vaccination for at least 90 days after treatment with monoclonal antibodies.)

The NIAID is funding clinical trials to assess vaccine response in people receiving immunosuppressive therapy and whether it can be easily and safely enhanced.

One is an open label study of kidney or liver transplant recipients who had no antibody titers after receiving 2 doses of the BNT162b2 or mRNA-1273 (Moderna) vaccine. All will receive a third dose of the same vaccine they’ve already had. However, some will be randomized to a temporary reduction in their standard immunosuppression regimen around the time they receive the third vaccine dose.

The chair of that study, Johns Hopkins transplant surgeon Dorry Segev, MD, PhD, recently coauthored a case series of 30 kidney transplant recipients’ response to COVID-19 vaccines. The researchers checked participants’ antibody titers 9 days before they received a third dose of vaccine and found that 24 of them had none. The authors then checked antibody titers an average of 14 days after participants’ third vaccine dose and found that 16 of the 24 who had none after 2 doses still didn’t have any, but 6 of them had high and 2 had low antibody titers.

Another NIAID-funded trial will test whether temporarily stopping immunosuppressive therapy around the time of vaccination could improve the response of people with autoimmune diseases such as rheumatoid arthritis or multiple sclerosis. This approach has been found to enhance immunogenicity of other vaccines, Rotrosen said.

“Immunocompromised comes in many sizes and shapes,” Myron Levin, MD, principal investigator of 2 phase 3 clinical trials of AZD7442, said in an interview. Levin is a pediatric infectious disease specialist at the University of Colorado.

One of the trials, PROVENT (A Phase III Randomized, Double-blind, Placebo-controlled, Multi-center Study in Adults to Determine the Safety and Efficacy of AZD7442 for Pre-exposure Prophylaxis of COVID-19), randomized 5197 unvaccinated adults in a 2 to 1 ratio to compare AZD7442 with placebo for preexposure prophylaxis. Only 196 of them had a compromised immune system, although more than 75% of trial participants had comorbidities such as obesity or cardiac disease that can diminish the immune response to COVID-19 vaccination, according to slides from AstraZeneca.

Detailed results have not yet been published, but AstraZeneca announced topline PROVENT results in an August press release. At IDWeek 2021 in late September, Levin reported that after following up study participants an average of 83 days and accruing a total of 25 cases, PROVENT met its primary efficacy end point with a 77% reduction in symptomatic COVID-19 among those who received AZD7442 compared with the placebo group. Rates of adverse events were similar between the 2 groups.
Exactly who should receive AZD7442 for preexposure prophylaxis is up to the FDA, noted Levin, who said he has never received funding from AstraZeneca for studying AZD7442. “I’m glad I don’t have to make those decisions.”

**Could Have, Should Have**

Pharmaceutical companies and the FDA could have speeded things up if they’d included a study group for preexposure prophylaxis in the postexposure prophylaxis trials, Rotrosen said.

Regeneron “fought very hard with FDA to have preexposure prophylaxis in the EUA,” Cohen noted, but with no data from people who hadn’t been exposed to SARS-CoV-2, the agency declined.

Yet, he pointed out, sorting out what constitutes preexposure or postexposure is difficult. “People can make arbitrary definitions,” Cohen explained.

In authorizing Regeneron’s monoclonal antibody cocktail for postexposure prophylaxis, the FDA said it could be given only to people at high risk of progression to severe COVID-19 who have been in close contact with an infected individual as defined by the CDC: less than 6 feet away for at least 15 minutes over a 24-hour period.

Those criteria “made a lot of sense” before the rise of the Delta variant, which is much more contagious than other SARS-CoV-2 variants, Rotrosen said.

Conducting preexposure prophylaxis trials will become more challenging after the FDA authorizes the first monoclonal antibody product for that use, he said.

“If the AstraZeneca product is approved for PrEP [preexposure prophylaxis], which seems likely, can you design a study for another PrEP product that has a placebo arm?” Rotrosen asked. Such a trial would probably require frequent testing of placebo group participants with polymerase chain reaction (PCR) to detect SARS-CoV-2 infection as soon as possible, at which point participants would have to be switched over to the monoclonal antibody group, Rotrosen said.

Although Regeneron’s monoclonal antibody cocktail has been authorized for preexposure and postexposure COVID-19 prophylaxis in the UK, patients can’t yet get it for that purpose. As of mid-October, the UK’s National Health Service had still limited its use to patients hospitalized with COVID-19, according to Claudia Schmitt, PhD, spokesperson for F. Hoffmann-La Roche Ltd in Basel, Switzerland, which markets the drug outside the US.

“We’ve been pushing the government here for a specific policy around immunocompromised patients,” Helen Rowntree, director of research, services, and engagement at the London-based charity Blood Cancer UK, said in an interview, noting that such individuals number about half a million in the UK.

**Taking Matters Into Their Own Arms**

Koffman, who was diagnosed with CLL in 2005 and cofounded the nonprofit CLL Society in 2013, hopes the FDA will grant AZD7442 an EUA for preexposure prophylaxis by year’s end.

But some people with compromised immune systems don’t want to wait that long. They’re checking their antibody titers and seeking a fourth vaccine dose, despite a lack of evidence for either. As Cohen pointed out, current antibody tests don’t specifically measure neutralizing antibodies, which prevent infection, and even if they did, it’s not clear what levels are protective.

“There is a sense of frustration from patient advocacy groups and patients themselves,” Marcus Pereira, MD, who established and directs the Transplant Infectious Diseases Program at New York-Presbyterian/Columbia University Irving Medical Center, noted in an interview, adding that a fully vaccinated patient with CLL had just died of COVID-19 at his hospital. “Patients are eager to be protected and go back to their normal lives.”

However, currently authorized antibody tests shouldn’t be used to evaluate immunity to SARS-CoV-2, especially after vaccination, according to the FDA.

“These tests of antibodies were not designed to tell you whether or not you were immune to COVID,” just whether a person had been infected with SARS-CoV-2 in the past, Pereira said. “The antibody is just one part of the immune system.”

When patients ask whether they should check their vaccine response with an antibody test, Pereira tells them that for now, they shouldn’t change their behavior based on whether the results are positive or negative. “Maintain all your safety precautions that you have done previously during the pandemic,” he advises. “I don’t want you to have a false sense of security. I also don’t want you to have a false sense of despair.”

Despite his warning about antibody tests’ lack of utility, “plenty of patients now are getting 4 [vaccine] doses because they had negative antibodies after 3 doses,” Pereira said. “What to do with these patients? Four doses? Five doses? Where does it end?”

In June, French health authorities began allowing a fourth vaccine injection to solid organ transplant recipients whose immune system didn’t respond after a third dose. However, kidney transplant recipients who generated no antibodies after a third vaccine dose were unlikely to generate any after a fourth vaccine dose, found a recent study by French researchers that had’t been peer-reviewed.

Koffman, who received AZD7442 in the PROVENT trial in January and then received the first of 3 BNT162b2 vaccine doses a few days later, noted that there’s currently no reason to check antibody titers because the tests aren’t standardized.

Nonetheless, he admits he couldn’t resist doing it, the first time about a month after his second vaccine dose and again after the third dose. “I’m kind of an information junkie, so I want to know every little bit,” Koffman explained. “My doctor did not recommend for it or against it.”

His antibody titers were far from zero, although the test couldn’t distinguish between antibodies resulting from being vaccinated or from the monoclonal antibodies he received in PROVENT, Koffman noted. He figures that’s better than having no antibodies, but just how much better isn’t yet clear.

So while he waits for the FDA to authorize monoclonal antibodies for preexposure prophylaxis, Koffman continues to limit get-togethers to socially distanced and masked backyard gatherings.

“Just because I have a good antibody level doesn’t mean that I’m protected,” he said. “Right now, our mantra is: Get vaccinated, but act as if you’re not vaccinated.”

**Conflict of Interest Disclosures:** Dr Koffman spoke at a recent press briefing about AZD7442, for which AstraZeneca made a contribution to the CLL Society. Dr Pereira reports serving as a study investigator for Moderna and Merck.

**Note:** Source references are available through embedded hyperlinks in the article text online.