cAMP, and there is a considerable body of evidence that PDE4 inhibitors are effective at inhibiting the proliferation and differentiation of fibroblasts as well as their ability to produce extracellular matrix in the presence of an endogenous or exogenous cAMP trigger. Studies in animal models of fibrosis across organ systems support the notion that PDE4 inhibition is antifibrotic, and preclinical studies showing that the preferential targeting of PDE4B by BI 1015550 (which was developed to overcome the well-known gastrointestinal side effects that are associated with broad PDE4 inhibition) provided support for the rationale to pursue this agent in the context of IPF.[8] In terms of influencing fibroblast function, BI 1015550 blocks mitogen-induced fibroblast proliferation and also acts synergistically with nintedanib to inhibit this response. However, unlike nintedanib, BI 1015550 also inhibits transforming growth factor β1–induced myofibroblast differentiation and extracellular-matrix expression,[8] a core fibrogenic pathway in multiple fibrotic conditions.[1]

In terms of the encouraging results of the current phase 2 trial, it is not possible to determine whether this agent exerts its potential beneficial effects by means of antiinflammatory, immunomodulatory, or multiple antifibrotic approaches or indeed by a combination of all these. However, together with the proven effectiveness of existing antifibrotic agents, which are likely to act on several targets or disease pathways, the continued exploration of agents that affect multiple collaborating mechanisms in IPF and potentially other fibrotic conditions continues to hold considerable promise.

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

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DOI: 10.1056/NEJMe2205411

Monoclonal Antibodies with Extended Half-Life to Prevent Covid-19

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Early treatment (i.e., soon after the onset of Covid-19 symptoms) with monoclonal antibodies that target the SARS-CoV-2 spike protein reduces the risks of Covid-19–related hospitalization and death.[1-3] Yet, despite the success of these interventions, in response to continued pressure from human immune responses, the SARS-CoV-2 spike protein has evolved to evade almost all available monoclonal antibody–based drugs.[4]

In this issue of the *Journal*, Levin et al.[5] report on the use of AZD7442 (tixagevimab–cilgavimab) for the prevention of Covid-19. Tixagevimab and cilgavimab are monoclonal antibodies that target the SARS-CoV-2 spike protein. Both were derived from B cells obtained from persons infected with SARS-CoV-2.[6] The non–antigen-binding fragment (Fc fragment) of these antibodies was modified so that they would have an extended half-life and decreased immune effector

functions.[7] The antibodies bind the spike-protein receptor-binding domain (RBD) and disrupt interactions with the cellular receptor of the virus, angiotensin-converting enzyme 2. Both were chosen to bind nonoverlapping RBD regions to better deal with the potential emergence of viral resistance mutations.[8]

After administration of the antibody pair, serum neutralizing titers are higher for up to 9 months than those usually detected in convalescent serum.[7] The monoclonal antibodies can also be detected in nasal mucosa, albeit in lower amounts than in serum.[7] The initially studied and recommended dose of 150 mg of each antibody was later increased by the Food and Drug Administration (FDA) to 300 mg of each antibody because of concerns about decreased activity against subvariants of the B.1.1.259 (omicron) variant.

As part of the ongoing phase 3 trial conducted by Levin et al., adults 18 years of age or older who were at increased risk for an inadequate response to Covid-19 vaccination, an increased risk of exposure to SARS-CoV-2, or both were enrolled and randomly assigned in a 2:1 ratio to receive a single dose (two consecutive intramuscular injections, one containing tixagevimab and the other containing cilgavimab) of 300 mg of AZD7442 or saline placebo, and they were followed for up to 183 days. The primary end point was symptomatic Covid-19 (with SARS-CoV-2 infection confirmed by means of reverse-transcriptase–polymerase-chain-reaction assay) occurring after administration of AZD7442 or placebo and on or before day 183.

Symptomatic Covid-19 occurred in 8 of 3441 participants (0.2%) in the AZD7442 group and in 17 of 1731 participants (1.0%) in the placebo group. This effect translates to a relative risk reduction of 76.7%. There were five cases of severe or critical Covid-19 and two Covid-19–related deaths, all in the placebo group.

The primary efficacy result in this trial is exciting, yet not unexpected. Providing antibodies as preexposure prophylaxis makes them directly available at the time at which the viral inoculum may be smallest. AZD7442 is thus much like a vaccine in which high titers of readily available neutralizing antibodies develop in all recipients.

However, the trial enrolled participants between late November 2020 and late March 2021, with the last participant receiving an injection on March 29, 2021. This period occurred well before the emergence of the BA.1 subvariant of the omicron variant — a variant of concern that is known to have a high level of antibody resistance. When viral genotypic data were available in the trial, the only variants of concern that were observed were B.1.1.7_1 (an alpha subvariant), B.1.351 (beta), and B.1.617.2 (delta). These previous variants contained a small number of RBD mutations (one to three) that left AZD7442 activity largely unaffected in cell-based assays.[7] The omicron BA.1 spike protein, however, contains 15 RBD mutations. The AZD7442 antibodies are differentially affected by omicron mutations in cell-based assays, and of the two antibodies, tixagevimab loses substantial activity against most omicron sublineages, whereas cilgavimab retains some activity.[4] For example, AZD7442 retains activity against BA.2 in cell-based assays, but this is mostly driven by cilgavimab activity.[4] Thus, against omicron sublineages, AZD7442 may behave more like a single monoclonal antibody (e.g., sotrovimab or bebtelovimab, which are used as single agents).

The extent to which losses of activity in cell-based assays will correlate with losses of efficacy in humans remains uncertain. In addition to blocking the entry of virus into cells, antibodies can harness immune effector functions. For example, a non-neutralizing antibody is included in a monoclonal antibody cocktail against Ebola virus disease.[9] However, the Fc fragments of AZD7442 antibodies were purposely engineered to dampen immune effector functions; thus, AZD7442 efficacy in humans may be vulnerable to spike-protein mutations that dampen the neutralizing activity of both components of the cocktail. Mutations to dampen immune effector functions were introduced to mitigate against possible antibody-dependent enhancement of disease. This phenomenon has not turned out to be a major concern in early treatment of Covid-19 with neutralizing antibodies. Thus, the removal of immune effector functions from the AZD7442 antibodies may represent a lost opportunity to enhance the efficacy of these antibodies against variants that resist antibody neutralization.

Given the considerable leap in spike-protein sequence evolution seen in omicron subvariants,

A video showing the activity of AZD7442 is available at NEJM.org

it is likely that they will outcompete all previous variants in a world in which most persons will probably have some degree of immunity to previous strains of SARS-CoV-2 elicited by natural infection, vaccination, or both. Omicron subvariants already contain an alphabet soup of RBD mutations (see the video, available with the full text of this editorial at NEJM.org), particularly in portions that fall within or near the footprint of both components of the AZD7442 cocktail. Of these changes, the one that should be most closely monitored is the R346K mutation, which is found in the BA.1.1 subvariant of the omicron variant and in B.1.621 (mu). The mutation would substantially decrease the activity of cilgavimab, which, as noted above, is the antibody that probably accounts for most of the retained activity against BA.2. In a recent preprint article, Case et al. reported that administration of AZD7442 to mice infected with BA.1.1 — which contains the R346K mutation — caused a decrease in viral RNA levels in the lungs by a factor of only four.[10] This effect is in stark contrast to the decrease by more than a factor of 400,000 seen with an ancestral strain of the virus (D614G) and a decrease by more than a factor of 100,000 seen with omicron BA.2 under the same circumstances.[10]

Although the FDA authorized the emergency use of AZD7442 for the prevention of Covid-19 in persons who have moderate-to-severe immune compromise due to a medical condition or who have received immunosuppressive treatments, of the participants in the current trial, only 0.5% had immunosuppressive disease, 3.3% were receiving immunosuppressive therapy at baseline, and 7.4% had cancer. It will be important to closely follow how AZD7442 performs in immunocompromised persons in a pandemic that has been dominated by dynamic variants that may gradually chip away at the activity of this antibody cocktail.

Continued evolution of the spike protein is the biggest threat to all monoclonal antibody–based interventions against SARS-CoV-2, and it can be stymied only by decreasing the total global burden of viral replication in human hosts. Although the shifting antigenic landscape of the spike protein may mean that monoclonal antibodies will require periodic updates, the ability to passively immunize persons who have an increased risk of an ineffective immune response is an important leap forward in the ongoing fight against viral evolution.

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DOI: 10.1056/NEJMe2205563