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NEWS ANALYSIS

Covid-19: Has the spread of omicron BA.2 made antibody treatments redundant?

Drug regulators are reviewing authorisations for monoclonal antibody treatments just months after they were issued. Elisabeth Mahase asks what the future holds for this class of biologicals

Elisabeth Mahase

The US Food and Drug Administration has removed its authorisation for anti-SARS-CoV-2 monoclonal antibody treatment sotrovimab because of concerns that it is ineffective against the omicron subvariant BA.2, which is now dominant in the US.[1]

The UK's Medicines and Healthcare Products Regulatory Agency (MHRA) authorised sotrovimab for high risk over 12s with mild to moderate covid-19 in December 2021[2] after reporting that a single dose, given as an intravenous infusion over 30 minutes, reduced the risk of hospital admission and death by 79% in high risk adults with symptomatic covid-19. The regulator has told *The BMJ* that it is also now reviewing the treatment to see if the "benefit-risk balance remains favourable."

Laura Squire, the MHRA's chief officer for healthcare access and quality, said, "We are in contact with the FDA and are looking closely at the data supporting their decision."

Developed by GlaxoSmithKline and Vir Biotechnology, sotrovimab is a single monoclonal antibody that works by binding to the SARS-CoV-2 spike protein, thereby preventing the virus from attaching to and entering human cells.

The drug was first authorised by the FDA in May 2021,[3] and the agency announced on 5 April 2022 that "the authorised dose of sotrovimab is unlikely to be effective against the BA.2 subvariant . . . Sotrovimab is not authorised in any US state or territory at this time."[1]

This is not the first time that authorisation for a covid-19 monoclonal antibody treatment has been affected by the spread of omicron. In January the FDA announced that, because of the high frequency of BA.1, both REGEN-COV (casirivimab and imdevimab) and the combination treatment of bamlanivimab and etesevimab were "not currently authorised for use in any US region because of markedly reduced activity against the omicron variant."[4 5]

Why don't these antibody treatments work against omicron?

Antibody treatments generally target and bind to the spike protein of SARS-CoV-2, an area of the virus highly susceptible to mutations. The BA.1 variant has 37 such spike mutations, while BA.2 has 31,[6] rendering some antibody treatments ineffective because they struggle to bind to and neutralise the virus.

Danny Altmann, immunologist at Imperial College London, said that while the focus on neutralising antibodies against specific parts of the SARS-CoV-2 spike had enabled several vaccines and treatments to be developed quickly during the pandemic, it also meant that the resulting protection strategy was vulnerable to new mutations and variants.

"We were all shocked last November, when we first saw the way in which the BA.1 mutations had taken out virtually all of the key neutralising epitopes targeted by vaccine induced antibody immunity, and BA.2 takes this a little further still," he said.

The adaptability of the virus has forced drug developers to rethink their strategy. Altmann says that researchers are now using "predictions from structural biology and monoclonal antibody technology" to develop broadly neutralising antibodies that can "surmount these evasive strategies, targeting parts of spike conserved across mutants."

Do any antibody treatments still work?

Eli Lilly's bebtelovimab has been shown to work against both BA.1 and BA.2.[7] Authorised by the FDA in February,[8] the treatment is for mild to moderate covid-19 in high risk people aged over 12.

In a statement the FDA said that it was "carefully monitoring circulating viral variants and their sensitivity to authorised monoclonal antibodies, including bebtelovimab. Laboratory testing showed that bebtelovimab retains activity against both the omicron variant [BA.1] and the BA.2 omicron subvariant."[8]

However, since bebtelovimab has not been evaluated in placebo controlled trials involving patients at high risk of progressing to severe covid-19, the FDA has said that it should be used only "when the preferred treatment options are not available, feasible to use, or clinically appropriate."[9]

Eli Lilly did not respond to queries from *The BMJ* as to why bebtelovimab remained effective against the BA.1 and BA.2 omicron variants.

What about Evusheld?

Despite being authorised by the MHRA on 17 March 2022, Evusheld (tixagevimab and cilgavimab) has not yet reached patients in the UK. The treatment was approved to prevent covid-19 in people unlikely to mount an immune response from vaccination or for

whom vaccination is not recommended, such as those who are immunocompromised or have blood cancer.[10]

Evusheld's manufacturer, AstraZeneca, reported in late March that the pre-exposure prophylactic retained "potent neutralising activity" against BA.1 and BA.2 in preclinical studies and that in infected mice it "significantly reduced the viral burden and limited inflammation in the lungs."[11]

However, the UK Health Security Agency does not seem convinced. A Department of Health and Social Care spokesperson has told *The BMJ* that the agency is "carrying out further testing on the treatment's effectiveness against the omicron variant [BA.2]" and that those results "will inform decisions on next steps including procurement."

Correction: On 25 April 2022 we removed the final paragraph, as it concerned a research preprint whose findings are no longer valid because they contained an error.

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