NEWS IN BRIEF

RSV antibody showcases passive immunotherapy progress

An antibody against the respiratory syncytial virus (RSV) could improve outcomes for this potentially fatal paediatric virus, show phase IIb results reported in the *New England Journal of Medicine*.

RSV is the most common cause of lower respiratory tract disease and hospitalizations for respiratory illness in infants and young children, and results in the hospitalization of nearly 100,000 young children in the United States alone each year. AstraZeneca's antibody palivizumab was approved as a prophylactic passive immunotherapy approach for RSV in 1998, making it the first and, as yet, only antibody approved for a virus. But the antibody, which binds the RSV envelope fusion protein, has a modest efficacy, a short half-life and high cost, which limit its utility. Other options are needed.

AstraZeneca and Sanofi's nirsevimab may now provide a better solution. In a phase IIb trial of the antibody versus placebo, in 1,453 pre-term infants, the incidence of medically attended RSV-associated lower respiratory tract infection was 70% lower with treatment than with placebo. Whereas palivizumab has to be administered monthly to achieve a protective effect of 45–55% in infants at high risk of RSV-related hospitalization, nirsevimab was administered once.

A phase III trial of the antibody in 3,000 healthy infants is ongoing, and the partners anticipate filing for approval in 2023.

Separately, Novavax reported phase III results from its recombinant RSV F protein nanoparticle vaccine ResVax. Rather than treating infants directly, Novavax's strategy is to vaccinate pregnant women to achieve passive immunity through the transfer of antibodies from mothers to their infants. This trial was the first ever phase III trial of a vaccine for maternal immunization licensure.

The trial enrolled 4,630 pregnant women, who received either vaccine or placebo at 28 to 36 weeks of gestation. The trial missed its primary end point, RSV-associated lower respiratory tract infection up to 90 days of life; with infection rates of 1.5% in the vaccine group and 2.4% in the placebo group, the vaccine offered an efficacy of 39%. Secondary end points, including hospitalization for RSV-associated disease, showed that the vaccine might reduce the severity of disease.

Novavax first disclosed this failure in March 2019. Regulators have since said that the company would have to run another phase III trial to secure approval. The company has yet to disclose next steps for the vaccine.

Paediatric infectious disease specialist Cody Meissner, at Tufts University School of Medicine, took an optimistic stance in a linked editorial. "Both approaches offer hope that an effective means for preventing RSV infections may finally be in sight," he wrote.

Others are also pursuing maternal immunization approaches for RSV. Pfizer's RSV vaccine PF-06928316 entered into phase III trials in pregnant women in June. GlaxoSmithKline's RSV vaccine GSK3888550A is set to enter phase III trials in pregnant women later this year.

Asher Mullard

Anti-IL-6Rs falter in COVID-19

Despite early hopes that the inhibition of signalling by the inflammatory cytokine IL-6 might hold potential in COVID-19, trial results are dampening enthusiasm.

Roche's latest trial results with its IL-6 receptor (IL-6R) antibody tocilizumab, reported at the end of July, show that the antibody failed to provide benefit in a phase III trial in 450 patients with severe COVID-19 associated pneumonia. The drug missed on its primary end point, the difference in clinical status between treatment and placebo, as well as on mortality at week 4. Weeks earlier, Regeneron and partner Sanofi reported that their IL-6R antibody sarilumab also failed in a phase III trial in critically ill COVID-19 patients on mechanical ventilation.

Preliminary evidence had suggested that these agents might be help control the cytokine release syndrome that has been linked to COVID-19. Tocilizumab is approved for cytokine release syndrome in response to CAR T cell treatment, and small studies, each in 20 patients or fewer, in China and France suggested that it improved outcomes in COVID-19.

A few trials of these agents, modulating a complex cytokine, are still ongoing. Roche's ongoing trials with tocilizumab in COVID-19 include a combination trial with Gilead's remdesivir. The RECOVERY trial, the UK-based platform trial that showed that dexamethasone has efficacy in severe disease, is also testing tocilizumab. And Sanofi is running a phase II/III trial of sarilumab in COVID-19 in critical patients, using a different dosing regimen of the drug. In April, the company amended this trial to discontinue enrolment of patients with less advanced 'severe' disease owing to lack of efficacy in this population. Johnson & Johnson's anti-IL-6 sirukumab is also in an ongoing trial in severe and critical COVID-19.

Asher Mullard

COVID-19 vaccine guidelines

With multiple COVID-19 vaccines in and approaching phase III trials, the FDA has released development and licensure guidelines for these products.

The 21-page guidelines detail agency recommendations on everything from manufacturing and preclinical data considerations to trial design, efficacy considerations and post-licensure safety.

On trial efficacy, the agency lists laboratory-confirmed COVID-19 and laboratory-confirmed SARS-CoV-2 infection as acceptable primary end points. It recommends that the primary end point or a secondary end point be defined as virologically confirmed SARS-CoV-2 infection, with one or more of several listed symptoms of disease. It also notes that, because a COVID-19 vaccine might be more effective in preventing severe versus mild COVID-19, "severe COVID-19 should be evaluated as a secondary end point … if not evaluated as a primary end point".

In terms of an efficacy thresholds, the agency calls for a primary efficacy end point point estimate of at least 50% protection.

The guidelines discuss possible surrogate end points, such as immune responses. But, it notes, "there are currently no accepted surrogate endpoints that are reasonably likely to predict clinical benefit of a COVID-19 vaccine". Development programmes should instead focus on traditional approval via direct evidence of vaccine safety and efficacy in protecting humans from SARS-CoV-2 infection and/or clinical disease, it recommends.

The guidelines also stipulate that the pre-licensure safety database for preventive vaccines should consist of at least 3,000 study participants. Follow up of study participants should continue as long as feasible, "ideally at least one to two years".

The ICMRA, a coalition of 30 regulatory bodies including the FDA and EMA, also recently published a summary of a workshop it held on regulatory requirements for COVID-19 vaccines. The ICMRA recommended that the primary end point should be laboratory-confirmed COVID-19 of any severity. The ICMRA has not as yet agreed on a specific numeric value for vaccine efficacy.

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