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Efficacy Analysis in Healthy-Volunteer Influenza Challenge Trials: Intention To Treat

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Healthy-human-volunteer influenza virus challenge models offer a unique setting to test novel therapeutics and vaccines. These studies play a key role in the development of influenza countermeasures (1) and will continue to do so. The paper "Phase 2 Randomized Trial of the Safety and Efficacy of MHAA4549A, a Broadly Neutralizing Monoclonal Antibody, in a Human Influenza A Virus Challenge Model" describes an influenza virus challenge study evaluating a novel monoclonal antibody targeting the hemagglutinin stalk (2). An intention-to-treat infected (ITTI) population excluded participants without detectable viral shedding or seroconversion. This postrandomization exclusion eliminated a significant number of participants from the primary analysis. This approach has previously been established as problematic and discussed in several publications in HIV research outlining the study design challenge of wanting to evaluate treatment only in infected individuals. These papers discuss the drawbacks of the ITTI approach and provide valid analyses incorporating data from all randomized participants (3–6).

In this study, 101 randomized participants were challenged. Ninety-nine participants began the assigned treatment (ITT population). Quantitative PCR (qPCR) data were obtained for 8 days for the primary endpoint of areas under the curve (AUC) of detectable virus in the nasopharynx. Given that the treatments being studied were expected to impact detectable virus, it is concerning that the ITTI population of 61 participants was determined by using this same qPCR data to exclude participants. By analyzing the ITTI population, the benefit of randomization is lost, as those defined as infected in the different intervention arms may be systematically different. Thus, the ITTI analysis may hide positive or negative effects on the overall (ITT) population, possibly resulting in misleading conclusions.

In an influenza virus challenge model, limitations in the number of laboratory-confirmed infections must be factored into the study design. Evaluating all subjects challenged, randomized, and treated allows group differences to be causally attributable to treatment. Using the authors' definition of a confirmed infection, the baseline rate in the placebo group was 66% (21/32). An effective treatment is expected to lower this rate. Rates of infection in the ITT population of this study were 55% (11/20), 65% (13/20), and 70% (14/20) for increasing doses of antibody and 25% (2/8) for oseltamivir. These rates suggest limited-to-no efficacy, which contradicts the main study conclusion that MHAA4549A was efficacious. The results of a true ITT analysis using the primary endpoint of AUC, with AUC equal to 0 for uninfected subjects, are more similar to those of an infection rate analysis. If the study was intended to evaluate MHAA4549A only in confirmed infections, a study design where randomization takes place after 2 positive

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qPCRs would provide unbiased results and reflect a more typical clinical trial design. Such a design reflects clinical practice where patients typically present with symptoms.

Significant investment in the development of novel influenza countermeasures is ongoing, and challenge studies will play a key role in their development. Analyses that allow for bias lead to uninterpretable results. Presenting such results can lead to erroneous efficacy conclusions and possible late-phase study failures or early abandonment of promising candidates. To maximize the value of these unique studies, applying statistical and scientific rigor is paramount.

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