Trials and tribulations of assessing safety

Assessing the causal relationship between AEs and a vaccine is extremely difficult in COVID-19 shots

The assessment and monitoring of safety during clinical trials is a vital component of developing COVID-19 vaccines. Expected local and systemic adverse reactions (AR), which characterize the reactogenicity of vaccines, are common. However, Adverse Events of Special Interest (AESI) are of major concern for regulatory authorities. US FDA defines an AESI (serious or non-serious) as one of the scientific and medical concerns specific to the sponsor's product or programme for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. AESI might require further investigation to characterize and understand it. Depending on the nature of AESI. rapid communication by the trial sponsor to other parties (e.g., regulators) might also be necessary.

For COVID-19, AESI includes serious events related to vaccination in general, to specific platforms, and to specific target diseases of COVID-19. AESI relevant to vaccination, in general, include 1) neurologic- Guillain-Barré Syndrome (GBS), acute disseminated encephalomyelitis 2) hematologic - thrombocytopenia 3) immunologic- anaphylaxis, vasculitis, arthritis, myocarditis and 4) Adverse Event Following Immunization (AEFI) - serious local/ systemic events. AESI relevant to specific vaccine platforms include aseptic meningitis/ encephalitis /encephalomyelitis, arthritis, and myocarditis. AESI related to specific target disease encompass manifestations of COVID-19 affecting immune, respiratory, CVS, hematologic, kidney, GI, CNS, and dermatology. Such pre-identified and predefined AESI have the potential to be causally associated with a vaccine and need to be carefully monitored and confirmed by further special studies.

FDA's Emergency Use Approval (EUA) of COVID-19 vaccines highlights the challenge of assessing AESI based on a review of short post-vaccination median follow-up of 7-8 weeks. The most common AR are: Injection site reactions, fatigue, headache, muscle pain, chills, joint pain, and fever. Severe AR and serious adverse events are not common. Myocardial infarction, cholecystitis, nephrolithiasis, appendicitis, and cerebrovascular accident were numerically higher in the vaccine group compared to the placebo group. The small numbers and the expected likelihood of such events in the general population did not suggest a causal relationship with the vaccine.

FDA also reviewed Bell's palsy reported in 7 participants – 6 in vaccine groups and 1 in placebo. Assessing the causal relationship between such AEs and a vaccines is extremely difficult. Phase III vaccine trials in 30,000-40,000 participants are not large enough to detect AEs less common than 1:10,000 participants reliably. However, if such uncommon AE is reported, information on background rate in the general population would be helpful in the evaluation of causality. As the annual incidence of Bell's palsy is 15-30 per 100,000, the number of cases reported in the trials did not appear to be more than that expected in the general population. However, considering the temporal association and biological plausibility, FDA opined that a potential contribution of the vaccine to the manifestations of these events of Bell's palsy cannot be ruled out.

It is essential for the sponsors to continue passive and active safety surveillance of AEFI and AESI in clinical trial participants and people receiving vaccine post-authorisation for several years for on-going evaluation of risks and benefits, and to support the maintenance of EUA and to obtain a license for wider use.

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