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Microbes and Infection 22 (2020) 403–404

Contents lists available at ScienceDirect

Microbes and Infection

journal homepage: www.elsevier.com/locate/micinf

Commentary

Coronavirus vaccine-associated lung immunopathology-what is the significance?

As an expanded number of coronavirus vaccines enter human clinical trials, in addition to understanding their efficacy in preventing severe SARS-CoV-2-related disease, a key outcome that will be receiving outsized scrutiny will be whether these vaccines contribute to lung immunopathology upon natural viral infection. Since the emergence of life-threatening severe acute respiratory syndrome (SARS) almost 20 years ago and subsequently Middle East respiratory syndrome (MERS) in 2012, numerous vaccines have been developed and tested in experimental animals to combat these lethal coronavirus-associated respiratory syndromes. An unexpected and concerning feature of several of these is the appearance of lung immunopathology that is seen in animals receiving certain types of vaccines. This result is especially concerning given that vaccine associated enhanced respiratory disease (VAERD) was seen in human vaccine trials against the ubiquitous airway pathogen respiratory syncytial virus (RSV). Although we must be mindful of potentially disappointing outcomes, a careful assessment of vaccine design, immunobiology, and clinical and experimental outcomes published thus far suggests that VAERD may not represent a major threat to ongoing vaccination efforts.

Lung immunopathology refers to exaggerated inflammation that envelopes the gas-exchanging units of the lung after viral infection and which may interfere with oxygenation. It is a concern because it can lead to worse disease than what would normally be seen after virus infection in the complete absence of vaccination. Clinical VAERD was first seen in human infants with RSV infection after receiving a formalin-inactivated vaccine against RSV in the 1960s that led to markedly worse respiratory disease as compared to non-vaccinated infants, in two cases leading to death [1]. The type of inflammation observed in RSV VAERD was also qualitatively different from that seen in natural infection. In suitable animal models of disease, RSV-related VAERD is characterized as a pulmonary “Arthus reaction” - infiltration of the lungs with neutrophils and lymphocytes as observed in a cotton rat model [2], or eosinophils observed in a Balb/c mouse model [3]. Histopathologic autopsy findings from an infant who died potentially of VAERD linked to RSV included monocytic pulmonary inflammation together with eosinophils [4].

Eosinophils are a type of infection-fighting cell of the immune system that are normally seen in parasitic and fungal infections or in unrelated non-communicable diseases such as asthma and inflammatory bowel disease. Although not proven, causal associations, eosinophilic lung immunopathology has been linked to multiple factors including 1) formalin alteration of vaccine antigens [1]; 2) complement activation [5]; and 3) T helper type 2 (Th2) and Th17 cell-predominant immune responses that coordinately drive the production and recruitment of eosinophils [6].

Because the immunopathology seen in experimental SARS and MERS coronavirus-related VAERD models was also eosinophilic, investigators have rightly raised concerns about the safety of coronavirus vaccines that will soon be tested in humans against COVID-19. However, beyond the fact that RSV is genetically distinct from coronaviruses, there are several additional differences between the vaccine-related VAERD that was seen in human RSV infection and that seen after experimental SARS and MERS vaccines. First, lethal vaccine-related immunopathology has only been seen in infants, who have immature immune systems that are less capable of mounting robust type 1 (i.e., interferon-dominated) immune responses as compared to adults. In general, type 1 immunity is required to overcome most viral infections and is readily generated in more mature individuals. Thus, RSV vaccine-related immunopathology may have had more to do with the immaturity of the infants’ immune system and less to do with vaccine-specific toxicity. This is supported by studies showing that older children do not experience immunopathology after RSV vaccinations [7,8], a study demonstrating that some RSV vaccines fail to induce antibody affinity maturation due to inadequate B cell activation, again a potential consequence of immaturity of the immune system [9], and studies of SARS vaccines in mature rodents. Regarding these latter studies, despite the emergence of eosinophilic immunopathology following infection, the animals all survived, in contrast to unvaccinated controls that all succumbed [10,11].

Second, eosinophilic immunopathology due to SARS infection occurred in vaccinated rodents despite their having abundant titers of neutralizing antibodies that, when present, normally preclude active infection [12]. One possible explanation for this paradoxical outcome is that experimental models of SARS infections as used in these studies involved viral exposures that likely far exceed natural exposures. Thus, in experimental contexts, viral exposures could be overwhelming vaccine-induced protective immunity, leading to an initial infection that, while inducing pathology, cannot propagate beyond a few rounds of viral reproduction and thus is ultimately self-limited. If this is true, then lung viral loads should be lower in vaccinated as compared to unvaccinated animals. In fact, mice receiving SARS vaccines that exhibited eosinophilic lung immunopathology demonstrated significantly lower lung viral titers within the first week of infection as compared to unvaccinated controls [10,12,13].

A third observation is that “immunopathology” as seen in experimental animals given different vaccine formulations appears to be

https://doi.org/10.1016/j.micinf.2020.06.007

quantitatively similar, although qualitatively dissimilar based on whether or not eosinophils predominate in the lungs. Although the adjuvant factor alum has been implicated in eosinophilic immunopathology, in fact this complication is seen with coronavirus vaccines both with and without alum; moreover, addition of alum appears to actually protect from eosinophilic lung pathology [12,14]. Regardless, these observations do not indicate that eosinophilia *per se* is harmful in this context.

While it is difficult to compare vaccines across their many different platforms and formulations, species tested in, and eras in which they were studied, a consistent, critically important issue appears to be the quality of the antibodies produced after vaccination. Early RSV vaccines failed to consistently induce neutralizing antibody responses [1] and careful follow-up studies now indicate that poor outcomes related to early RSV vaccines were indeed due to inadequate generation of neutralizing antibodies [9]. Moreover, it is clear from animal studies that vaccination leads to survival regardless of the type of immunopathology as long as neutralizing antibodies are produced [10–12].

These observations give us hope that naturally occurring COVID-19 infections, typically involving fewer virions initially acquired as compared to experimental infections, will be short-lived and rapidly controlled in properly vaccinated individuals. Such individuals may in fact remain asymptomatic and never know they were infected. It is furthermore possible that the fate of naturally acquired SARS-CoV-2 virus in properly vaccinated individuals will simply be neutralization, with the virus never initiating either infection or immunopathology. This is based on the robust protection against SARS-CoV reinfection afforded mice receiving a recombinant protein-based vaccine [15] and rhesus macaques that received an inactivated SARS-CoV-2 vaccine formulated with alum [16]. Additional findings confirm that SARS-CoV-2 vaccine-induced protection in rhesus macaques correlates with the generation of high titers of neutralizing antibodies [17]. We should always be prepared to find and avoid vaccine-related complications such as lung immunopathology. Nonetheless, the available data indicate that the best way to avoid this complication-and defeat SARS-related coronaviruses-is through vaccines that generate robust neutralizing antibodies.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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18 June 2020
Available online 26 June 2020