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EDITORIAL

Autoimmune Hepatitis-Like Syndrome Following COVID-19 Vaccination: Real or Imagined?

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Introduction

When a new vaccine is administered over a short time period to millions of individuals, any adverse event that follows can be presumed to be an effect of the vaccine [1]. It is difficult, however, to establish with certainty a causal relationship between vaccination and adverse events, with few possible exceptions such as anaphylaxis and vaccine-strain infections after live viral vaccination. For decades, a variety of vaccines have been implicated in eliciting an autoimmune response, some with credible evidence supporting causality (e.g., diphtheria toxin and Guillain-Barré syndrome (GBS), MMR vaccination and thrombocytopenic purpura) [2], and others in which extensive review has failed to demonstrate a causal link (e.g., hepatitis B vaccine and multiple sclerosis) [3].

In the phase III clinical trials leading to the emergency use authorization (EUA) of COVID-19 vaccines in the United States, serious autoimmune disorders were considered when reporting adverse events of clinical interest. Though no significant autoimmune events were found in the Pfizer-BioNTech or Moderna trials, embolic and thrombotic events were noted in the Johnson & Johnson/Janssen (J&J) phase III clinical trial. Following authorization of the J&J vaccine, several cases of thrombosis with thrombocytopenia syndrome, an immune-mediated phenomenon similar to heparin-induced thrombocytopenia, led to a temporary pause in the use of the J&J vaccine in April, 2021 [4]. The FDA resumed use of the J&J vaccine soon after, citing a thorough risk–benefit assessment. Since then, other immune-mediated events have been reported correlated with COVID-19 vaccinations, including GBS from the J&J vaccine [5] and immune thrombocytopenia from the mRNA vaccines [6] Among these extremely rare but potentially linked effects of the COVID-19 vaccines is a growing number of cases of presumed autoimmune hepatitis (AIH) that were temporally associated with COVID-19 vaccination.

In this issue of *Digestive Diseases and Sciences*, Chow et al. report their systematic review of "autoimmune hepatitis-like syndrome" following COVID-19 vaccination [7]. They discuss case reports and series involving 32 patients with an autoimmune hepatitis-like syndrome following an mRNA or Oxford-AstraZeneca COVID-19 vaccine. In the ongoing COVID-19 pandemic, with over 10 billion vaccine doses administered [8], it is essential to closely examine any liver-related events following COVID-19 vaccination, however rare they may be. As the global medical library continues to accumulate similar cases, reports such as the one by Chow et al. can help other providers understand the varied presentations and management strategies of a new phenomenon. An even finer look at the details of each case in this systematic review reveals three distinct, but related, clinical entities.

The first entity appears as a typical drug-induced liver injury (DILI), comprised of those patients who develop clinical hepatitis (hepatocellular or cholestatic) following vaccination without features of an autoimmune process**.** The case by Lodato et al. provides one such example [9]. Though the authors in this report did not calculate an International Autoimmune Hepatitis Group (IAIHG) score [10], the absence of autoantibodies, normal immunoglobulin G levels, and histology with predominant eosinophils and a lack of plasma cells suggest against an autoimmune drug-induced liver injury (AI-DILI). In the series by Shroff et al. [11], excluding four patients with known AIH, 11 of the remaining 12 did not meet the simplified IAIHG criteria for "probable" or "definite" AIH. It remains unknown whether these patients require immunosuppressive therapy or simply

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can be observed for improvement. Indeed, many of the patients in these reports recovered spontaneously without any treatment.

A second entity describes relapse of previously diagnosed AIH. In the series by Shroff et al., four of the sixteen patients had an existing history of AIH. Although all four were in clinical remission prior to vaccination, immune stimulatory events, including infections or vaccinations, may induce a relapse of previously stable AIH [12]. Indeed, another case that fits this description was recently published [13]. In these situations, management will mirror that of a typical AIH flare, with a brief corticosteroid re-induction and possible adjustment of maintenance immunosuppression.

The remaining clinical entity describes the cohort of patients who have a more definite presentation of an AI-DILI, or in this case, a vaccine-induced AIH. All of these patients met IAIHG criteria for an autoimmune process, with no other identifiable triggers aside from preceding COVID-19 vaccination. Although most cases of true AIH are defined by the absence of a cause (i.e., "idiopathic"), there has been extensive research into pathogenic triggers. Reports suggest that 9% of individuals have well-defined drug triggers (e.g., minocycline, nitrofurantoin) [14]. Clinically, patients with AI-DILI respond well to corticosteroids and overwhelmingly do not relapse after immunosuppression withdrawal. Longer term follow-up of the patients in the present series can illuminate whether the same prognosis is true in situations of COVID-19 vaccine-induced AIH.

Though on the surface the cases compiled by Chow et al. may appear similar, on a finer analysis of the details, important features emerge that facilitate the understanding of differing prognoses and management strategies, including whether permanent immunosuppression is required or whether certain groups can be safely re-challenged with the vaccine.

It is important to reiterate the possibility of correlation (rather than causality) that has already been stated by Chow et al. and others before in all analyses of suspected drug-induced disease. Application of the known baseline incidence of AIH (approximately 1 case per 100,000) [15] to the >10 billion patients who have been vaccinated for COVID-19 yields a large number of individuals who would be expected to develop de novo AIH over the span of the pandemic, whether or not they were vaccinated. Even if a causal link is presumed between the COVID-19 vaccines and AIH, these cases are exceedingly rare and almost always resolve completely, with or without treatment. As Chow et al. appropriately conclude, these reports should not discourage COVID-19 vaccination.

While causality may be nearly impossible to ascertain without additional rigorous study, studies such as the one by Chow et al. and the cases that informed their systematic review should be further pursued. The public relies on the collective vigilance of the medical community as a necessary measure in order to ensure the greatest degree of safety and evidence-based practice in novel clinical circumstances.

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