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Research letter

Association of herpes zoster with COVID-19 vaccination: A systematic review and meta-analysis

To the Editor: Herpes zoster (HZ), which is reactivation of the varicella zoster virus (VZV), is associated with older age, use of immunomodulatory drugs, trauma, family history, and other comorbidities.[1] Moreover, case studies have reported development of HZ following administration of vaccinations against influenza, Japanese encephalitis, hepatitis A, and rabies.[2] Recently, several cases of HZ after COVID-19 vaccinations have been reported[1]; however, the association remains a matter of debate due to the small number of cases and lack of control groups.

We performed a systematic search within PubMed, EMBASE, and Web of Science for relevant publications from inception to November 2022 following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The protocol was registered in PROSPERO (CRD42023381589). Cohort studies, case-control cross-sectional studies, and randomized controlled trials reporting HZ outcomes in patients receiving COVID-19 vaccinations and control subjects were included. Studies with overlapping cases, lack of HZ outcomes, incomplete data, and case studies without controls were excluded (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/6jg7jkn65r/1). This meta-analysis (MA) used a random-effects model to calculate the pooled odds ratios (ORs) and 95% CIs to determine the risk of HZ in the COVID-19 vaccination group versus control groups. Subgroup analyses comparing the risk of HZ in the mRNA versus adenovirus vaccination groups and Moderna versus BioNTech vaccination groups were performed. Sixteen studies were included from initially identified 465 articles (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/6jg7jkn65r/1). COVID-19 vaccination was associated with a significantly increased risk of HZ (OR, 1.32; 95% CI, 1.09-1.62, $P = .006$) compared with controls (Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/6jg7jkn65r/1). In subgroup analysis, the mRNA vaccination was associated with a higher risk of HZ compared with the adenovirus vaccination (OR, 1.67; 95% CI, 1.19-2.35, $P = .003$) (Supplementary Fig 3, available via Mendeley at https://data.mendeley.com/datasets/6jg7jkn65r/1). Further MA of studies comparing different brands of COVID-19 vaccinations showed no significant difference of HZ risks between Moderna and BioNTech (OR, 0.64; 95% CI, 0.18-2.21) (Supplementary Fig 4, available via Mendeley at https://data.mendeley.com/datasets/6jg7jkn65r/1).

The mechanism underlying the link between COVID-19 vaccination and HZ remains elusive; however, vaccination-induced immunomodulation has been proposed. Vaccine-induced massive shift of $CD8^+$ T cells and $CD4^+$ helper T cells may cause temporary inability to suppress latent VZV, allowing for its reactivation.[3] Previous studies indicate that immunocompromised status and older age are associated with a higher risk of VZV reactivations after vaccination.[4] The reported median time to onset of HZ after COVID-19 vaccination was 7 to 10 days (range, 2-51 days).[1,4,5] Although most cases of VZV reactivations were dermatome-limited, 2 cases of HZ infection after COVID-19 mRNA vaccination were disseminated.[5] Our research has limitations. First, because most randomized controlled trials of COVID-19 vaccination did not report HZ as a separate individual adverse effect, the number of randomized controlled trials included in this MA is quite limited. Second, heterogeneity exists among the included studies, and the quality of the included studies is not very high (Supplementary Fig 5, available via Mendeley at https://data.mendeley.com/datasets/6jg7jkn65r/1). Nevertheless, our MA suggests an increased risk of HZ in patients receiving COVID-19 vaccination, and the mRNA vaccination is associated with a higher risk of HZ than the adenovirus vaccination. This highlights the awareness of possible reactivation of HZ following COVID-19 vaccination, particularly for high-risk individuals.

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Conflicts of interest

H.Y.C. received speaking fees from AbbVie, Novartis Pharmaceuticals Corporation, Janssen-Cilag Pharmaceutica, Eli-Lilly, Kyowa Hakko Kirin Taiwan, and Pfizer Limited and conducted clinical trials for Eli-Lilly, AbbVie, and Sanofi Pharmaceuticals. I.L.C. has no conflicts of interest to declare.

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