Research letter

Evaluating risk of bullous pemphigoid after mRNA COVID-19 vaccination

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Dear Editor, Approximately 3·3 billion people across the globe are fully vaccinated against COVID-19. However, there remains a significant proportion of populations who are experiencing vaccine hesitancy, for reasons that can include concern about vaccine-induced autoimmunity. Bullous pemphigoid, the most common autoimmune blistering skin disease, has been reported as a rare side-effect of mRNA COVID-19 vaccines.[1,2] Proposed mechanisms involve nonspecific bystander immune activation, molecular mimicry, and in the context of the COVID-19 pandemic, a novel consequence of mRNA vaccine technology.[1,2] In this study, we evaluated the relationship between *de novo* development of bullous pemphigoid and mRNA COVID-19 vaccination in a large global health research network.

We performed a retrospective cohort study using the TriNetX analytics network (trinetx.com; Cambridge, MA, USA), a federated health research network that aggregates health records from 63 healthcare organizations, compromising 70 million patients. We included people ≥18 years of age who between 15 December 2020 and 15 June 2021 received either a first or second dose of the Moderna (mRNA-1273) or Pfizer/BioNTech (BNT162b2) vaccine (cases) or were diagnosed with acne, seborrhoeic keratosis or melanocytic naevi and had no history of COVID-19 vaccination (controls). We agreed that diagnoses included in the control cohort were to be conditions with no known association with bullous pemphigoid. Multiple diagnoses were included to increase cohort size for robust propensity matching. Data collection was performed in December 2021 to ensure all participants had an opportunity for 24 weeks of follow-up. New-onset bullous pemphigoid (ICD-10 code L12·0) related to mRNA COVID-19 vaccine administration was defined as the first-ever diagnosis occurring within 24 weeks. People with pemphigus vulgaris (ICD-10 code L10·0) were excluded from both cohorts to increase the positive predictive value of bullous pemphigoid diagnosis.[3]

We balanced the cohorts using 1 : 1 greedy, nearest-neighbour propensity score, matching by age, sex, race, ethnicity, neurological disease (Parkinson disease, demyelinating disease, other degenerative disorders of the nervous system), psychiatric disease (mood disorders, schizophrenia), cerebral infarction and malignancy, as well as use of dipeptidyl peptidase-4 inhibitors (linagliptin, alogliptin, sitagliptin, saxagliptin), checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab, ipilimumab), loop diuretics and spironolactone. Two dermatologists, who were experienced in evaluating bullous pemphigoid, independently agreed on risk factors, based on literature review, to be included in the propensity-matched analysis.[4,5] Given that participants may have been vaccinated outside of the healthcare organizations included in the database, a subgroup analysis was performed against a historical cohort compromised of individuals who received the control diagnoses between 1 January 2020 and 1 December 2020, to assess risk in a population wherein COVID-19 vaccination was not available. Using the matched cohorts, we calculated the relative risk (RR) of first appearance of bullous pemphigoid in the 24 weeks after index events in the respective cohorts. All statistical analyses were performed within TriNetX.

We identified 1 540 234 people who received a dose of the mRNA COVID-19 vaccine. The mean (standard deviation) age in the mRNA COVID-19 vaccine cohort was 54·7 (18·5) years, 13% of participants were black, 64% were white, 10% were Hispanic or Latino and 6% were Asian. Prior to matching, the crude incidence of bullous pemphigoid within 24 weeks of mRNA COVID-19 vaccination was 0·004% (57 of 1 539 720). After 1 : 1 propensity matching, demographic and clinical characteristics were balanced (standard deviation <0·1). No difference in risk of new-onset bullous pemphigoid was observed among participants receiving the mRNA COVID-19 vaccine within 24 weeks compared to either the control cohort (RR 0·77, 95% confidence interval 0·37–1·57) or the historical cohort (RR 0·55, 95% confidence interval 0·30–1·02) (Table 1).

Our results suggest mRNA COVID-19 vaccination is not associated with increased risk of new-onset bullous pemphigoid. We hope that healthcare professionals may use the findings reported herein to counsel patients experiencing vaccine hesitancy over concerns of *de novo* autoimmunity. Our study has limitations to consider when interpreting the results. Firstly, our study reports on the risk of new-onset bullous pemphigoid and does not offer insight regarding whether vaccination can cause a flare or an exacerbation of the disease. In addition, risk of bullous pemphigoid may differ between the first or second dose of mRNA COVID-19 vaccine or by Moderna vs. Pfizer vaccination, but we did not investigate this in our report. Other limitations to consider include the use of population data, which have inherent misclassification bias from the use of ICD codes. We cannot ascertain completeness of electronic medical records. Lastly, participants may have developed bullous pemphigoid without seeking care.

Table 1 Risk of bullous pemphigoid after mRNA COVID-19 vaccination

Cohort	Participants in cohort[a]	Participants with bullous pemphigoid	Rate (per 10 000 person-years)[b]	Risk ratio (95% CI)
mRNA COVID-19 vaccination vs. control cohort				
Vaccination	238 755	13	1·2	0·77 (0·37–1·57)
Control	238 710	17	1·5	
mRNA COVID-19 vaccination vs. historical cohort				
Vaccination	415 840	16	0·8	0·55 (0·30–1·02)
Control	415 739	29	1·5	

The relative risk compares the risk of bullous pemphigoid within 24 weeks after mRNA COVID-19 vaccination against participants in control cohorts after matching for age, sex, race, ethnicity, neurological disease (Parkinson disease, demyelinating disease, other degenerative disorders of the nervous system), psychiatric disease (mood disorders, schizophrenia), cerebral infarction and malignancy, as well as use of dipeptidyl peptidase-4 inhibitors (linagliptin, alogliptin, sitagliptin, saxagliptin), checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab, ipilimumab), loop diuretics and spironolactone. CI, confidence interval. [a]Participants with outcome prior to the time window were excluded from results. [b]Rates per 10 000 person-years were calculated as follows: [(persons with bullous pemphigoid)/(persons in cohort)] × (365/168) × 10 000.

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Conflicts of interest: the authors declare they have no conflicts of interest.

Data Availability Statement: The data that support the findings of this study are available from TriNetX Restrictions apply to the availability of these data, which were used under license for this study. Data are available MB with the permission of TriNetX