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Vaccine-Associated Uveitis after COVID-19 Vaccination

Vaccine Adverse Event Reporting System Database Analysis

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Purpose: To assess the risk of vaccine-associated uveitis (VAU) after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination and evaluate uveitis onset interval and clinical presentations in the patients.

Design: A retrospective study from December 11, 2020, to May 9, 2022, using the Centers for Disease Control and Prevention Vaccine Adverse Event Reporting System.

Participants: Patients diagnosed with VAU after administration of BNT162b2 (Pfizer-BioNTech, Pfizer Inc/BioNTech SE), mRNA-1273 (Moderna, Moderna Therapeutics Inc), and Ad26.COV2.S (Janssen, Janssen Pharmaceuticals) vaccine worldwide.

Methods: A descriptive analysis of the demographics, clinical history, and presentation was performed. We evaluated the correlation among the 3 vaccines and continuous and categorical variables. A post hoc analysis was performed between uveitis onset interval after vaccination and age, dose, and vaccine type. Finally, a 30-day risk analysis for VAU onset postvaccination was performed.

Main Outcome Measures: The estimated global crude reporting rate, observed to expected ratio of VAU in the United States, associated ocular and systemic presentations, and onset duration.

Results: A total of 1094 cases of VAU were reported from 40 countries with an estimated crude reporting rate (per million doses) of 0.57, 0.44, and 0.35 for BNT162b2, mRNA-1273, and Ad26.COV2.S, respectively. The observed to expected ratio of VAU was comparable for BNT162b2 (0.023), mRNA-1273 (0.025), and Ad26.COV2.S (0.027). Most cases of VAU were reported in patients who received BNT162b2 (n = 853, 77.97%). The mean age of patients with VAU was 46.24 ± 16.93 years, and 68.65% (n = 751) were women. Most cases were reported after the first dose (n = 452, 41.32%) and within the first week (n = 591, 54.02%) of the vaccination. The onset interval for VAU was significantly longer in patients who received mRNA-1273 (21.22 ± 42.74 days) compared with BNT162b2 (11.42 ± 23.16 days) and rAd26.COV2.S (12.69 ± 16.02 days) vaccines ($P < 0.0001$). The post hoc analysis revealed a significantly shorter interval of onset for the BNT162b2 compared with the mRNA 1273 vaccine ($P < 0.0001$). The 30-day risk analysis showed a significant difference among the 3 vaccines ($P < 0.0001$).

Conclusions: The low crude reporting rate and observed to expected ratio suggest a low safety concern for VAU. This study provides insights into a possible temporal association between reported VAU events and SARS-CoV-2 vaccines; however, further investigations are required to delineate the associated immunological mechanisms. *Ophthalmology 2022;■:1–8 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

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The global coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to swift vaccine development and approval. Since the beginning of the pandemic, 336 vaccine candidates have been developed, and 32 vaccines are currently authorized for use globally.[1] On December 11, 2020, the first vaccine received emergency use authorization from the US Food and Drug Administration (FDA) for a large-scale vaccination program to prevent the spread of SARS-CoV-2 and reduce its severity in infected patients.[2] Among the authorized vaccines, BNT162b2 (Pfizer Inc/BioNTech SE) and mRNA-1273 (Moderna Therapeutics Inc) are based on messenger RNA (mRNA), whereas Ad26.COV2.S (Janssen Pharmaceuticals) uses a recombinant replication-incompetent adenovirus type 26 vector to stimulate an immune response in the recipients.[3–5] Because all the SARS-CoV-2 vaccines were approved for emergency use authorization, the Centers for

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Disease Control and Prevention (CDC) expanded the purview of its Vaccine Adverse Event Reporting System (VAERS), a passive surveillance platform that functions as an early warning system for potential vaccine adverse events.[6] Several ophthalmic disorders, including uveitis, were added as the adverse events of interest to the system.

Several reports in the literature have highlighted the temporal association between uveitis and universally administered vaccines, such as hepatitis B, human papilloma virus, influenza, Bacille Calmette–Guérin, measles, mumps, and rubella, and varicella vaccines.[7–13] Benage and Fraunfelder[14] identified 289 cases of vaccine-associated uveitis (VAU) published in the literature and reported by the surveillance systems (including VAERS) over 26 years. Although the precise immunopathological mechanisms that cause VAU are yet to be delineated, several hypotheses attribute it to the immune response to vaccine adjuvants, molecular mimicry between vaccine peptide fragments and uveal self-peptides, and delayed hypersensitivity and subsequent immune complex deposition as the potential causes.[15–18] As of June 2022, uveitis is one of the most commonly reported ophthalmic adverse events after SARS-CoV-2 vaccination, with >70 published reports and case series.[19]

Since the initiation of the most extensive vaccination program, several studies have evaluated the safety concern of inflammatory disorders (e.g., Guillain–Barré syndrome, myocarditis) after SARS-CoV-2 vaccination using the VAERS database.[20–26] For a comprehensive insight into the potential association between VAU and the 3 FDA emergency use authorized COVID-19 vaccines (BNT162b2, mRNA-1273, and Ad26.COV2.S), we analyzed the largest cohort of VAU cases using the VAERS database. Herein, we determine the global crude reporting rate and the observed-expected ratio of uveitis since the initiation of the vaccination program. We also report the clinical characteristics in patients diagnosed with VAU and assess the association between demographics and duration of uveitis onset after vaccination.

Methods

Data Source

This retrospective cohort study was conducted using the CDC-VAERS database (CDC, Atlanta, GA). The VAERS is the national early warning system that monitors the safety of vaccines after they are authorized or licensed for use by the FDA. The database is publicly available, deidentified, anonymous data of vaccine-related adverse events reported by patients, parents (for minor patients), clinicians, vaccine manufacturers, and regulatory bodies worldwide. The VAERS data are available through the Wide-Ranging Online Data for Epidemiologic Research platform, developed and operated by the CDC.[27] The database includes demographic information, date of vaccination and adverse event onset, brief medical and surgical history, current comorbidities and medications, history of adverse events, and a detailed report of the clinical signs and symptoms and the diagnoses of the adverse events postvaccination. All the reports submitted to VAERS that appear to be false or fabricated to mislead the CDC and FDA are reviewed before being added to the VAERS database. A false VAERS report violates Federal law (18 U.S. Code § 1001) and is punishable by a fine and imprisonment. The reports are then evaluated by third-party professional coders, who assign appropriate medical terminology using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms based on the unstructured data in the submitted reports.[28] On requesting explicit permission to analyze and publish these data, we were informed that CDC Wide-Ranging Online Data for Epidemiologic Research allows access to the information freely and use, copy, distribution, or publication of this information without additional or explicit permission.[29] This study was conducted in compliance with the tenets of the Declaration of Helsinki and the National Statement on Ethical Conduct in Human Research 2007. Because the study includes publicly available, deidentified, anonymous data, the University of Adelaide Human Research Ethics Committee exempted it from ethical review.

Study Population

The patients diagnosed with VAU who received BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines between December 11, 2020, and May 9, 2022, were included in the study. The VAU cases were reported from 40 countries, and the data from the United States were reported from 40 of the 50 states and 1 overseas territory. The data query included VAU reported in patients of all ages and genders categorized by VAERS (based on MedDRA) into uveitis (uncategorized), autoimmune uveitis, Behçet's syndrome, chorioretinitis, choroiditis, herpes ophthalmicus, intermediate uveitis, iridocyclitis, keratouveitis, tubulointerstitial nephritis and uveitis syndrome, and uveitis-glaucoma-hyphaema syndrome. The data provided by the VAERS were grouped by symptoms, age, sex, state (in the United States)/overseas territory, and onset interval. The additional measures included in the data curation were adverse event description, laboratory data, current illness, adverse events after prior vaccination, medications at the time of vaccination, and allergies. The locations of the patients reporting from overseas territories were estimated on the basis of the standardized ISO code used by VAERS to categorize these data. The data points of interest were manually extracted (by R.B.S., U.P.S.P., and F.K.) from the unstructured adverse event descriptions for analysis.

Statistical Analysis

The statistical analysis was performed using R Studio (R Foundation for Statistical Computing). The crude reporting rates were estimated using the number of VAU reports (by vaccine type) per million COVID-19 vaccine doses. The 30-day observed to expected ratios for the cases in the United States were calculated using the formula − (person-years × background rate)/100 000, where background rates were measured per 100 000 person-years. The person-years at risk for uveitis within 30 days of vaccination were calculated as the number of persons who received at least 1 vaccine dose × 30/365.25. The assessment of the observed-expected ratio analysis was limited to reports from the United States because of the lack of accurate global vaccination data and background rates of uveitis, which are highly variable in different populations. The background rate for the US population was referenced from the study reporting the incidence rate of uveitis in the United States by Acharya et al.[30] The total number of vaccinated individuals and the doses administered in the United States during the study period were obtained from the publicly accessible CDC data.[31]

A descriptive analysis of the social demographic characteristics and vaccination data was performed. We assessed the association between the onset interval of uveitis and vaccine type, age, sex, and dosage using the 1-way analysis of variance test. Because the history of COVID-19, uveitis and other inflammatory disorders, and ocular and systemic presentations were categorical variables, a Pearson chi-square test of association was performed to evaluate the risk associated with the 3 vaccines. A post hoc analysis was performed to evaluate the variability in VAU onset duration in the age groups, dose, and vaccine type. A reverse Kaplan–Meier risk analysis was also performed for the 3 vaccines. The missing values in the data were indicated, and the Na.rm code accounted for them during the analysis. The value of $P < 0.05$ was considered statistically significant.

Results

During the study period, 2 061 557 270 doses of BNT162b2 (1 499 560 544; 80.7%), mRNA-1273 (501 950 217, 16.8%), and Ad26.COV2.S (60 046 509, 2.5%) were administered.[2] A total of 1 250 310 (0.06% of all doses) adverse events after vaccinations were recorded in the CDC-VAERS, including 1094 reports of VAU. The mean age of the patients was 46.24 ± 16.93 years, and the majority were female (68.65%). The demographic data of the patients are summarized in Table 1. The cases were reported from countries in Australasia (38, 3.47%), Asia (61, 5.58%) Europe (685, 62.61%), North America (291, 26.60%), and South America (3, 0.27%). Because the 3 vaccines (BNT162b2, mRNA-1273, and Ad26.COV2.S) were widely adopted for the vaccination programs in the countries in North America and Europe, a considerably higher proportion of VAU cases were reported from these regions compared with Asia, Australasia, and South America, where other vaccines are being administered. The country-wise distribution data of the cases are reported in Table S1 (available at www.aaojournal.org). The crude reporting rate for each of the countries could not be calculated because of the lack of stratified data for the 3 vaccine types. In the United States, 281 cases of VAU were reported, and the state-wise distribution and crude reporting rate are outlined in Table S2 (available at www.aaojournal.org).

The estimated crude reporting rates (per million doses) for BNT162b2, mRNA-1273, and Ad26.COV2.S were 0.57, 0.44, and 0.35, respectively. The observed to expected ratios of VAU in the United States were comparable for BNT162b2 (0.023), mRNA-1273 (0.025), and Ad26.COV2.S (0.027). Most of the patients in the study cohort had received the BNT162b2 vaccine (853, 77.9%), and the remaining patients were administered mRNA-1273 (220, 20.1%) and Ad26.COV2.S (21, 1.9%) vaccines. Vaccine-associated uveitis was reported in 452 patients (41.32%) after the first dose, 373 patients (34.1%) after the second dose, 97 patients (8.87%) after the third dose, and 5 patients (0.46%) after the fourth dose. Expectedly, few cases were reported after the booster (third and fourth) doses because few people have been vaccinated beyond the initial protocol at the time of conducting this study. In the cohort, 54.02% of patients were diagnosed with VAU within the first week of receiving the vaccine, including 17.01% on the day of vaccination. The onset interval was delayed (>7 days) in 357 patients (32.63%) and unknown in the remaining 146 patients (13.35%). The mean and median onset duration were 13.52 ± 28.63 and 4 days, respectively.

The 1-way analysis of variance showed a significantly shorter duration of VAU onset in patients who received BNT162b2 (11.42 ± 23.16 days, $P < 0.0001$) compared with mRNA-1273 (21.22 ± 42.74 days) and Ad26.COV2.S (12.69 ± 16.02 days). There was no significant difference in the VAU onset between the sexes and age groups. However, a significant difference was observed in the onset interval between different vaccine dosages ($P = 0.0009$). Additionally, the mean onset interval was longest in patients diagnosed with VAU after the second dose (18.89 ± 33.82 days). The analyses evaluating the association of onset interval with vaccine type, sex, age, and dosage are summarized in Table 2.

Table 1. Demographics of Patients Who Were Reported with Uveitis after Coronavirus Disease 2019 Vaccination

	Frequency (n)	%
Mean age (yrs)	46.24 ± 16.93	
Age, yrs		
5–12	12	1.10
13–18	38	3.47
19–65	821	75.05
>65	144	13.16
Unknown	79	7.22
Sex		
Female	751	68.65
Male	322	29.43
Unknown	21	1.9
Origin		
Australasia*	38	3.47
Asia	61	5.58
Europe	685	62.61
North America	291	26.60
South America	3	0.27
Unknown	16	1.46

*Australia and New Zealand.

Table 2. Analysis to Assess the Factors Associated with Onset Interval of Uveitis after Coronavirus Disease 2019 Vaccination

	Percentage (n)	Mean Onset Interval (days)	*P* Value
Vaccine*			
BNT162b2	77.97% (853/1094)	11.42 ± 23.16	**<0.0001**
mRNA-1273	20.11% (220/1094)	21.22 ± 42.74	
Ad26.COV2.S	1.92% (21/1094)	12.69 ± 16.02	
Sex*			
Female	68.65% (751/1094)	13.35 ± 28.65	0.647
Male	29.43% (322/1094)	14.19 ± 29.05	
Unknown	1.9% (21/1094)		
Age*			
5–12	1.10% (12/1094)	10.11 ± 16.62	0.062
13–18	3.47% (38/1094)	15.96 ± 22.82	
19–65	75.05% (821/1094)	12.61 ± 26.44	
>65	13.16% (144/1094)	19.79 ± 41.32	
Unknown	7.22% (79/1094)		
Dosage*			
1	41.32% (452/1094)	11.05 ± 24.81	**0.0009**
2	34.1% (373/1094)	18.89 ± 33.82	
3	8.87% (97/1094)	9.97 ± 29.06	
4	0.46% (5/1094)	1.75 ± 2.87	
Unknown	15.27% (167/1094)		

*One-way analysis of variance test performed. The significant values where $P < 0.05$ appear in bold.

Table 3. Analysis of Association among History, Ocular Presentation and Diagnosis, and Systemic Presentations with the 3 Vaccines

	Vaccine (Frequency and Percentage)				
	BNT162b2	*mRNA-1273*	*Ad26.COV2.S*	**P Value**	**Chi-Square**
History					
COVID-19	0.7% (6/853)	0.9% (2/220)	4.76% (1/21)	0.124	4.162
Uveitis	10.2% (87/853)	7.7% (17/220)	9.5% (2/21)	0.542	1.222
Systemic autoimmune diseases	1.17% (10/853)	1.8% (4/220)	0	0.652	0.855
Ocular presentation					
Eye pain	22.97% (196/853)	30% (66/220)	38.1% (8/21)	**0.034**	6.712
Ocular redness	79.84% (681/853)	65.9% (145/220)	61.9% (13/21)	**<0.0001**	21.59
Reduced vision	24.03% (205/853)	25.9% (57/220)	0	**0.048**	6.053
Photophobia	7.5% (64/853)	13.1% (29/220)	9.5% (2/21)	**0.028**	7.131
Floaters	1.17% (10/853)	5% (11/220)	0	**0.0008**	14.02
Lacrimation	1.99% (17/853)	2.3% (5/220)	0	0.775	0.5088
Ocular diagnosis					
Anterior uveitis	45.1% (385/853)	44.1% (97/220)	52.4% (9/21)	0.307	2.272
Iritis	3.04% (26/853)	3.6% (8/220)	0	0.641	0.8877
Iridocyclitis	22% (188/853)	17.27% (38/220)	4.76% (1/21)	0.0565	5.745
Ocular herpes	22% (188/853)	24.1% (53/220)	38.1% (8/21)	0.193	3.282
HLA B27	3.4% (29/853)	3.2% (7/220)	0	0.102	4.341
Posterior uveitis	4.5% (38/853)	4.1% (9/220)	4.8% (1/21)	0.742	0.342
Chorioretinitis	2.9% (25/853)	2.3% (5/220)	4.8% (1/21)	0.674	0.786
Retinitis	2.3% (22/853)	3.6% (8/220)	4.8% (1/21)	0.606	0.459
Choroiditis	1.4% (12/853)	0	0	1	0
Panuveitis	10.1% (86/853)	10% (22/220)	4.8% (1/21)	0.723	0.647
Behçet's disease	7.0% (60/853)	5.5% (12/220)	4.8% (1/21)	0.661	0.826
VKH	0.6% (5/853)	0.5% (1/220)	0	0.916	0.173
Systemic symptoms					
Fever	13.7% (117/853)	14.1% (31/220)	19% (4/21)	0.78	0.495
Headache	11.3% (96/853)	13.6% (30/220)	9.5% (2/21)	0.589	1.058
Mucosal ulcerations	4.9% (40/853)	7.7% (17/220)	14.2% (3/21)	**0.042**	4.134
Arthritis	5.0% (43/853)	7.3% (16/220)	9.5% (2/21)	0.318	2.288
Systemic diagnosis					
Ankylosing spondylitis	1.3% (11/853)	0.5% (1/220)	0	0.506	1.361
Sarcoidosis	1.2% (10/853)	0	4.8% (1/21)	0.065	5.45
Multiple sclerosis	0.2% (2/853)	0	0	1	0
SLE	0.3% (3/853)	0.9% (2/220)	0	0.524	1.292
Thyroiditis	0.2% (2/853)	0	0	1	0
Inflammatory bowel disease	0.1% (1/853)	0	0	1	0

COVID-19 = coronavirus disease 2019; HLA = human leukocyte antigen; SLE = systemic lupus erythematosus; VKH =Vogt-Koyanagi-Harada disease. The significant values where $P < 0.05$ appear in bold.

Among the patients diagnosed with VAU, few had a history of COVID-19 infection (9, 0.8%), uveitis (106, 9.6%), or systemic autoimmune diseases (14, 1.2%). At presentation, few patients were on immunosuppressant drugs such as dexamethasone (12, 1.1%), prednisolone (8, 0.73%), mycophenolate mofetil (6, 0.55%), cyclosporine (6, 0.55%), azathioprine (4, 0.37%), infliximab (4, 0.37%), and rituximab (2, 0.18%), and 1 patient each had been prescribed tacrolimus, leflunomide, and risankizumab. Ocular pain was reported by a significantly higher proportion of patients who had received the Ad26.COV2.S vaccine (38.1%, $P = 0.034$) compared with the other 2 vaccines, whereas hyperemia was reported more commonly in patients who received BNT162b2 (79.84%, $P < 0.0001$). A significantly higher proportion of patients who presented with reduced vision (25.9%, $P = 0.048$), photophobia (13.1%, $P = 0.028$), and floaters (5%, $P = 0.0008$) had received mRNA-1273 vaccine compared with BNT162b2 and Ad26.COV2.S vaccines. In the cohort, 491 patients (44.88%) were diagnosed with anterior uveitis, among whom 249 (22.76%) had

Table 4. Post Hoc Analysis Comparing Onset Interval in Patients of Different Age Groups

Age (yrs)	**5–12**	**13–18**	**19–65**	**>65**
5–12	1			
13–18	0.983	1		
19–65	0.998	0.973	1	
>65	0.862	0.967	0.056	1

Table 5. Post Hoc Analysis Comparing Onset Interval with Different Vaccine Doses

	First Dose	**Second Dose**	**Third Dose**	**Fourth Dose**
First dose	1			
Second dose	0.0021	1		
Third dose	0.9974	0.0621	1	
Fourth dose	0.966	0.7519	0.979	1

Table 6. Post Hoc Analysis Comparing Onset Interval in Patients Who Received BNT162b2 (Pfizer), mRNA-1273 (Moderna), and Ad26.COV2.S (Janssen)

	BNT162b2	mRNA-1273	Ad26.COV2.S
BNT162b2	1		
mRNA-1273	**<0.0001**	1	
Ad26.COV2.S	0.9860	0.5457	1

The significant values where $P < 0.05$ appear in bold.

herpes ophthalmicus, 227 (20.74%) had iridocyclitis, and 34 (3.14%) had iritis. Panuveitis was diagnosed in 109 patients (9.96%). The number of patients diagnosed with anterior, posterior, and panuveitis was comparable for 3 vaccines. Fever (152, 13.89%), headache (128, 11.70%), mucosal ulcerations (60, 5.48%), and arthritis (61, 5.57%) were the most common systemic presentations. A significantly higher proportion of patients who were vaccinated with Ad26.COV2.S vaccine presented with mucosal ulcerations ($P = 0.042$). The ocular and systemic presentations of VAU patients are detailed in Table 3.

The post hoc analysis between the different doses and VAU onset showed a significant difference between the onset intervals of the first and second doses ($P = 0.021$). We also found the VAU onset interval was significantly shorter in patients who received the BNT162b2 vaccine compared with mRNA-1273 vaccines. The post hoc analyses between onset interval and age groups, vaccine type, and dose are detailed in Tables 4 to 6. The 30-day reverse Kaplan–Meier risk analysis showed a higher risk of VAU with BNT16b2 compared with mRNA-1273 and Ad26.COV2.S vaccines ($P < 0.0001$) (Fig 1).

Discussion

The initiation of the vaccination program to immunize people against SARS-CoV-2 was a critical step in managing the COVID-19 pandemic, which has impacted every nation worldwide. The 3 FDA emergency use authorized vaccines (BNT162b2, mRNA-1273, and Ad26.COV2.S) have shown high efficacy against SARS-CoV-2 and significantly reduced the incidence of severe disease, hospitalizations, and long-term effects of this respiratory virus.[32–34] Because these vaccines were given emergency use authorization by the FDA, without the data on the short-term and long-term adverse effects, several concerns were raised about the potential systemic adverse effects, including ocular disorders. The population-based studies have reported several adverse events possibly associated with these vaccines, including pericarditis, arrhythmia, deep vein thrombosis, pulmonary embolism, myocardial infarction, intracranial hemorrhage, and thrombocytopenia; however, the evidence of VAU after SARS-CoV-2 vaccination is limited to a few case reports and series.[19,33–36] Only one large-scale database study from Israel, including 188 patients with noninfectious uveitis after SARS-CoV-2 vaccination, was recently published.[37]

Several years ago, Aguirre et al[38] reported the generation of a uveitic reaction in a canine model on injecting adenovirus 1, which was attributed to the type III hypersensitivity response due to generation of antigen-antibody complexes in the aqueous humor. Recent studies have reported the detection of SARS-CoV-2 RNA in the aqueous humor and other ocular tissues of patients infected with the virus, leading to a similar inflammatory response involving immune complex deposition.[39,40] Because BNT162b2 and mRNA-1273 are mRNA delivery vaccine platforms, it can be speculated that a viral mRNA-induced immune response may be causing VUA in some patients postvaccination. On the contrary, Rabinovitch et al[41] attributed VAU caused by mRNA vaccines to type I immune response leading to elevated levels of interferons.[42] They suggested that the mRNA delivery through the vaccines leads to the activation of RNA-sensing molecules (TLR3, TLR7, MDA5, and RIG-I), leading to activation of autoimmune processes in these patients. However, it has been reported that modified nucleobase (N1-methylpseudouridine) added to the SARS-CoV-2

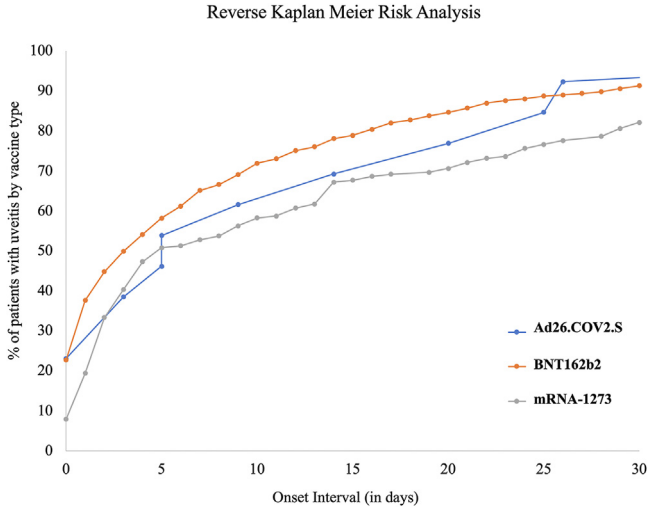

Figure 1. Kaplan–Meier risk analysis showed a higher risk of VAU with BNT16b2 compared with mRNA-1273 and Ad26.COV2.S vaccines. VAU = vaccine-associated uveitis.

vaccines suppresses the vaccine-induced immunostimulatory response.[43] The Ad26.COV2.S vaccine is a replication-incompetent recombinant adenovirus type 26 viral vector that expresses SARS-CoV-2 spike protein.[5] In the past, Cunningham et al[18] have attributed delayed-type hypersensitivity and immune responses observed in VAU to the molecular similarities between uveal self-peptides and vaccine peptides. However, the suggested mechanisms that cause the VAU after SARS-CoV-2 vaccines are purely speculative and require further investigation.

In the literature, several VAU cases have been reported after SARS-CoV-2 vaccination. In the only large-scale study evaluating VAU, Tomkins-Netzer et al[37] reported 100 and 88 cases of noninfectious uveitis within 21 days of first and second dose post-BNT162b2 vaccination, respectively. In our study cohort, we also observed that approximately 75% of the patients were diagnosed with VAU within the first month of vaccination, and more cases were reported after the first dose (41.32%) compared with the second dose (34.1%). In the study conducted by Tomkins-Netzer et al,[37] the majority of the patients had a history of uveitis (52%) and were diagnosed with anterior uveitis (90.96%) after vaccination. In the cases reported to VAERS, few patients with VAU had been previously diagnosed with uveitis (9.7%) or systemic autoimmune diseases (1.2%), and only 44.9% of the cases were diagnosed with anterior uveitis after vaccination.

Study Limitations

This study reporting the VAU cases after SARS-CoV-2 vaccination has several limitations. The VAERS is a passive surveillance system that records adverse event reports from pharmaceutical companies, physicians, drug regulators, and patients globally. Despite the mandatory requirement to report vaccine-associated adverse events, underreporting and delayed reporting are common. In some cases, the submitted reports are incomplete and lack uniformity in data reporting, and several reports have missing data points, such as ethnicity, that are considered important risk factors associated with uveitis.[44–47] The VAERS data are broadly stratified into uveitis (uncategorized), autoimmune uveitis, Behçet's syndrome, chorioretinitis, choroiditis, herpes ophthalmicus, intermediate uveitis, iridocyclitis, keratouveitis, tubulointerstitial nephritis and uveitis syndrome, and uveitis-glaucoma-hyphaema syndrome on the basis of MedDRA definitions, limiting the insight into the clinical diagnosis in these patients. The data reported in this study only suggest a temporal relationship between uveitis onset and SARS-CoV-2 vaccination and do not demonstrate a causal relationship. Further investigations are required to establish a causal relationship.

The absence of an unvaccinated control group limits the assessment of the relative risk of uveitis postvaccination. The pharmacovigilance associated with SARS-CoV-2 vaccines is limited to the European Union, the United States, Australia, Canada, and a few Asian countries. Thus, the reports are not recorded from many developing countries where $>$ 1 billion doses of vaccines have been administered. Moreover, the data are absent for several approved vaccines, such as ChAdOx1 nCoV-19, ZyCoV-D, Sputnik, Covidecia, Sputnik, Sinopharm, Abdala, Soberna, Zifivax, and Novavax, which are not in use in the United States.

Conclusions

The analysis of the largest adverse event global database suggests that the 3 vaccines BNT162b2, mRNA-1273, and Ad26.COV2.S rarely cause VAU. However, most of the patients diagnosed with VAU had anterior uveitis and received the BNT162b2 vaccine. Vaccine-associated uveitis was primarily diagnosed after the first dose and within the first week after vaccination. The benefits of vaccination outweigh the risk of VAU, but physicians should be aware that there is a possibility of VAU and seek prompt referral to an ophthalmologist if there is a suspicion for uveitis after vaccination.

Footnotes and Disclosures

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Abbreviations and Acronyms:
CDC = Centers for Disease Control and Prevention; **COVID-19** = Coronavirus Disease 2019; **FDA** = Food and Drug Administration; **MedDRA** = Medical Dictionary for Regulatory Activities; **mRNA** = messenger RNA; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **VAERS** = Vaccine Adverse Event Reporting System; **VAU** = vaccine-associated uveitis.

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