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Research Article

Vaccines and Corneal Graft Rejection

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Received: February 18, 2021; **Published:** March 31, 2021

Abstract

A retrospective case series to report a possible signal between vaccinations and corneal graft rejection (CGR). Post-marketing drug surveillance were reviewed for possible vaccine related CGR. In addition, a literature search using "vaccine" and "corneal graft rejection" was performed. Global online medical and life sciences media services were also reviewed. There were 25 possible vaccine related CGR in 22 eyes of 19 patients. Median age was 67 years. Onset post-vaccination to CGR had a median of 14 days. There were 3 positive rechallenges with a median time to onset of 14 days and 1 positive double rechallenge. There were 3 bilateral CGR with 2 occurring in both eyes within 24 hours after vaccination and 1 second eye CGR occurring within 72 hours of the first eye. Nineteen eyes recovered with steroids, 3 went on to graft failure, and there was no follow-up data in the remaining 3 cases. This data suggests a signal that requires future large data analysis to determine if, in a small subset of patients, vaccines may cause CGR. Ophthalmologists may consider asking CGR patients about their last 2-month vaccination history. Prophylactic steroids may be considered in these patients when future vaccinations occur.

Keywords: *Vaccine; Vaccination; Corneal Graft Rejection; Corneal Graft Failure*

Abbreviations

CGR: Corneal Graft Rejection; WHO: World Health Organization; ICSR: Individual Case Safety Reports; AVR: Adverse Vaccine Reaction

Introduction

Vaccine-related corneal graft rejection (CGR) case reports have been reported [1-5]. These case reports are not mentioned in corneal textbooks or encyclopedic websites; however, they are mentioned in corneal surgeon web sites and their discussion group (www.cornea-society.org).

Post-marketing surveillance data is the primary area of signals as to possible adverse ocular side effects from vaccines [6]. The largest databases for post-marketing drug surveillance are VigiBase (the World Health Organization [WHO] global database of Individual Case Safety Reports [ICSR]) and the Vaccine Adverse Event Reporting System managed by the U.S. Centers for Disease Control and Prevention and the U.S. Food and Drug Administration to monitor the safety of all vaccines licensed in the U.S. [7,8].

Purpose of the Study

The purpose of this is to add 10 additional cases of possible vaccine-associated CGR and to evaluate these reports along with the literature as to a possible weak signal between CGR and vaccines. A signal implies that enough data has been presented that is judged to be of sufficient likelihood to justify verificatory action. Regardless, in the rare instance of a CGR within a few weeks of a vaccination it may be prudent to use some prophylactic measures. This may be timely with a projected 1+ billion COVID-19 vaccinations anticipated in the near future.

Materials and Methods

This study was reviewed by the Institutional Review Board of Oregon Health and Science University and was determined to be exempt for Human Research. We adhered to the ethical principles outlined in the Declaration of Helsinki as amended in 2013 and all research was HIPAA compliant [9]. The data was evaluated by the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Portland, OR).

A retrospective observational case series of ICSR from VigiBase and the Vaccine Adverse Event Reporting System for all vaccines was completed in July 2020 with the earliest case from 2009. A literature search using keywords "vaccine" and "corneal graft rejection" was performed and the earliest case was from 1988 [1]. An additional case was reported on a global online medical and life sciences media service [5]. Data garnered from these sources include vaccine type, gender, age, adverse vaccine reaction (AVR), dosage, duration of therapy until onset of AVR, dechallenge and rechallenge data. The drugs recorded on the ICSR were coded according to the WHO Drug and the Medical Dictionary for Regulatory Activities was used to specify the adverse effects in this study. An attempt was made to identify a pattern with this AVR using onset time, progression, dechallenge, rechallenge, speed of recovery, and type of vaccine.

Results

There were 25 possible vaccine-related CGR in 22 eyes of 19 patients, including 3 positive rechallenge (Table 1). Thirteen CGR were from the literature, 10 were from VigiBase with additional details from the Vaccine Adverse Event Reporting System and 2 were from a media service. All CGR were associated with the influenza vaccine except for 1 with the varicella zoster vaccine, 1 with a combination of pneumococcal and tick-borne encephalitis vaccines and 1 with tetanus toxoid booster followed by 2 later hepatitis B immunizations. Of the CGR associated with the influenza vaccine, 10 were with an inactivated influenza vaccine, 8 could not be determined [1,3] and 2 were with a live vaccine. There were 13 females and 6 males. Ages ranged from 24 to 84 years with an average of 57 years (median 67 years). There was no pattern of time of first vaccination to when a CGR occurred with a later vaccination; the longest being the 12th annual vaccination [2].

	Source	Age	Sex	Vaccine	Time to Onset of CGR Post-Vaccination	Outcome
1	WHO VigiBase/VAERS	Approx. 70	M	Herpes zoster vaccine	Less than 1 year	Not recovered
2	WHO VigiBase	67	F	Influenza vaccine	UNK	Recovered
3	WHO VigiBase	33	M	Influenza vaccine	UNK	Recovered
4	WHO VigiBase	82	F	Influenza A (H1N1) vaccine	15 days	Recovered
5	WHO VigiBase/VAERS	51	M	Influenza vaccine	8 days	UNK
6	WHO VigiBase/VAERS	24	M	Influenza vaccine	8 days	Recovered
7	WHO VigiBase/VAERs	63	M	Influenza vaccine	2 days	UNK

8 9	WHO VigiBase/VAERS[a]	25	F	Influenza A (H1N1) vaccine	1 day OS 1 day OD	Recovered UNK
10	WHO VigiBase	66	F	Pneumococcal vaccine Tick-borne encephalitis vaccine	5 days	Recovered
11 12	Solomon[2a]	80	F	Influenza vaccine	42 days OS 45 days OD	Recovered Recovered
13	Hamilton[4]	33	M	Influenza vaccine	21 days	Recovered
14	Wertheim[3]	67	F	Influenza vaccine	14 days	Recovered
15 16	Wertheim[3bc]	67	F	Influenza vaccine Influenza vaccine	21 days 28 days (rechallenge)	Recovered Recovered
17	Steinemann[1]	84	F	Influenza vaccine	35 days	Recovered
18	Steinemann[1]	73	F	Influenza vaccine	30 days	Not recovered
19	Steinemann[1]	69	F	Influenza vaccine	56 days	Not recovered
20	Steinemann[1]	72	F	Influenza vaccine	21 days	Recovered
21 22 23	Steinemann[1c]	33	F	Tetanus toxoid booster Hepatitis B vaccine (part 1) Hepatitis B vaccine (part 2)	6 days 1 day (rechallenge) 14 days (rechallenge)	Recovered Recovered Recovered
24 25	Goldman[5a]	25	F	Influenza A (H1N1) vaccine	1 day OS 1 day OD	Recovered Recovered

Table 1: *Corneal graft rejections following vaccinations.*
a: Bilateral Graft Rejection, b: Deep Anterior Lamellar Keratopathy (DALK), c: Positive Rechallenge.

The known time to onset of post-vaccination CGR varied from 1 to 56 days with an average of 17 days (median 14 days). The time to onset of the 3 positive rechallenges varied from 1 to 28 days with an average of 14.3 days (median 14 days). In the 3 cases of bilateral CGR, the graft rejection occurred in the first eye within 1 day, 1 day, and 42 days after vaccination. The onset of the second eye CGR all occurred within 3 days, with 2 occurring on the same day as the first eye. Nineteen of the 25 CGR returned to normal after steroid therapy, 3 went on to graft failure, and in 3 CGR the outcome was unknown.

The CGR usually fully recovered with steroids, however there were 3 graft failures, one of which the vaccination may have possibly only hastened its demise [2]. There is data suggesting that a second eye corneal transplant may cause a bilateral CGR. The time of onset of the bilateral CGR was 4 to 12 days (5 cases) and 4 to 203 days (13 cases) with a median of 90 days [10,11]. In our series of 3 bilateral CGR, 2 of the second eyes occurred on the same day as the first and the other occurred within 3 days of the first (Table 1).

Discussion and Conclusion

The reasons these case reports may indicate a possible signal include: a plausible time period of the AVR after vaccination, a pattern with positive dechallenge and rechallenge data, a plausible immunologic mechanism, double positive rechallenge, and 3 patients having bilateral CGR after a vaccination with 2 occurring within 24 hours of an influenza vaccination. The eye may be a target for vaccine-induced immunological responses such as oculorespiratory syndrome [12]. This syndrome was originally described when using a swine flu adjuvant. Now, with newer vaccines without this adjuvant, it is only occasionally reported in spontaneous reporting systems. This

small subset of patients suggests a possible ocular immune response. This syndrome occurs within 2 to 24 hours and resolves within 48 hours. It consists of bilateral conjunctivitis, edema, decreased vision, and discharge. Specific cytokines (IL-10 and IL-3) have shown to be persistently elevated in this syndrome suggesting an immunologic response to the influenza vaccine [13]. Miller-Fisher syndrome leading to extraocular muscle paralysis has been associated with influenza vaccines. The mechanism is probably that anti-GQ1b antibodies in conjunction with activated complement components are the principal pathophysiological mediators affecting the ocular motor system [14]. There have been numerous case reports attributing various possible immunologic mechanisms of influenza vaccines causing uveitis, optic nerve disease, and retinitis [15]. None have been proven.

Drawbacks of AVRs include incomplete data, multiple observers, limited follow-up, unsubstantiated data, errors, variations of vaccine strains, adjuvants, and various other vaccine components over time. There are over 200,000 corneal grafts performed globally each year [16]. The majority of these probably had multiple vaccine exposures after grafts. With this large denominator and small numerator, the cases presented could be a chance association and not a signal. Still, there is a high probability that patients with a CGR were not asked about vaccine exposure.

Inactivated influenza vaccines have been generally well tolerated in solid organ transplant recipients [17,18]. A literature review concluded no convincing epidemiological link between vaccinations and allograft dysfunction [19]. However, these patients were on significant immunosuppression drugs, a situation uncommon in most corneal transplant patients. Stulting., *et al*. in a cohort study within a multicenter randomized clinical trial, found that in 571 cases of endothelial keratoplasty there was no increase in endothelial rejection in those who had flu vaccinations within 3 months of corneal surgery compared to those in the nonvaccinated within 3-month group [20]. This scientific study is encouraging, however only includes endothelial keratopathy and the numbers are small to find a rare event.

This observational study cannot prove an association only large epidemiological monitoring systems can define the value of this possible signal. If a CGR occurs after a vaccination, then one may want to consider the possible recommendations in Table 2. No one knows what effect COVID-19 vaccines will have on the eye. The clinician should have a higher awareness of a possible association of any vaccine and CGR because each CGR may increase endothelial cell stress and subsequent graft failures.

1.	Consider vaccines as a possible signal causing CGRs in a very rare subset of individuals.
2.	This possible signal may be stronger in patients with prior AVR, patients with autoimmune disease, and in high-risk corneal graft patients (especially vascularized grafts).
3.	Ask patients with a recent CGR if they had any recent vaccinations within the past 2 months. If so, consider starting prophylactic ocular steroids 2 days before and for 2-3 weeks after their next vaccination.
4.	Consider waiting 2 months after a vaccination before performing a corneal graft in high-risk corneal graft patients.

Table 2: *Recommendations (Modified from references 1-5).*

The Uppsala Monitoring Center and the Vaccine Adverse Event Reporting System have provided the data, which was reviewed by the National Registry of Drug-Induced Ocular Side Effects, but the study results and conclusions are those of the authors and not those of the Uppsala Monitoring Center, National Centers, or WHO [6]. The Vaccine Adverse Event Reporting System cannot determine if a vaccine caused an AVR and can only determine if further investigation is needed [8].

The National Registry of Drug-Induced Ocular Side Effects (www.eyedrugregistry.com) welcomes any of your case reports to better document this possible AVR.

Acknowledgements

Bree Jensvold-Vetsch, B.S., provided editing services during the preparation of the manuscript.

Conflict of Interest

No financial interest or conflict of interest exists.

Bibliography

1. Steinemann TL., *et al*. "Corneal allograft rejection following immunization". *American Journal of Ophthalmology* 106.5 (1988): 575-578.

2. Solomon A. and Frucht-Pery J. "Bilateral simultaneous corneal graft rejection after influenza vaccination". *American Journal of Ophthalmology* 121.6 (1996): 708-709.

3. Wertheim MS., *et al*. "Corneal transplant rejection following influenza vaccination". *British Journal of Ophthalmology* 90.7 (2006): 925.

4. Hamilton A., *et al*. "Stromal rejection in a deep anterior lamellar keratoplasty following influenza vaccination". *Clinical and Experimental Ophthalmology* 43.9 (2015): 838-839.

5. Goldman DA. and Etter J. "Refractive surgery and vaccines" (2020).

6. Edwards IR. and Biriell C. "Harmonisation in pharmacovigilance". *Drug Safety* 10 (1994): 93-102.

7. Uppsala Monitoring Centre. "Caveat document: statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICRs)" (2020).

8. "Vaccine adverse event reporting system (VAERS)" (2020).

9. World Medical Association. "World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects". *JAMA* 310.20 (2013): 2191-2194.

10. Khodadoust AA and Karnema Y. "Corneal grafts in the second eye". *Cornea* 3.1 (1984): 17-20.

11. Donshik PC., *et al*. "Effect of bilateral and unilateral grafts on the incidence of rejections in keratoconus". *American Journal of Ophthalmology* 87.6 (1979): 823-826.

12. Skowronski DM., *et al*. "Oculo-respiratory syndrome: a new influenza vaccine-associated adverse event?" *Clinical Infectious Diseases* 36.6 (2003): 705-713.

13. Al-Dabbagh M., *et al*. "Elevated inflammatory mediators in adults with oculorespiratory syndrome following influenza immunizations: a public health agency of Canada/Canadian Institutes of Health Research Influenza Research Network Study". *Clinical and Vaccine Immunology* 20.8 (2013): 1108-1114.

14. Plomp JJ., *et al*. "Miller Fisher anti-GQ1b antibodies: alpha-latrotoxin-like effects on motor end plates". *Annals of Neurology* 45.2 (1999): 189-199.

15. Fraunfelder FT and Fraunfelder FW. "Influenza virus vaccine". Drug-Induced Ocular Side Effects, 8th Edition, edited by Bree Jensvold-Vetsch, Elsevier (2020): 386-387.

16. Gain P., *et al*. "Global survey of corneal transplantation and eye banking". *JAMA Ophthalmology* 134.2 (2016): 167-173.

17. Gangappa S., *et al*. "Kinetics of antibody response to influenza vaccination in renal transplant recipients". *Transplant Immunology* 53 (2019): 51-60.

18. Khishgsuren B., *et al*. "Panel reactive antibody responses against influenza vaccination in kidney transplant recipients". *Transplantation Proceedings* 51.4 (2019): 1115-1117.

19. Kumer D., *et al*. "Influenza vaccination in the organ transplant recipient: review and summary recommendations". *American Journal of Transplantation* 11.10 (2011): 2020-2030.

20. Stulting RD., *et al*. "Factors associated with graft rejections in the Cornea Preservation Time Study". *American Journal of Ophthalmology* 196 (2018): 197-207.

Volume 12 Issue 4 April 2021