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REVIEW ARTICLE

Acute corneal allograft rejection following SARS-CoV-2 vaccination–A systematic review

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Abstract

All documented cases of acute corneal allograft rejection following SARS-CoV-2 vaccination were examined, to characterize possible risk factors and graft outcomes. Comprehensive search (4 electronic databases: PubMed, CENTRAL, ClinicalTrials.gov, Google Scholar, plus manual search in articles' reference lists) until March 1st 2022 to identify studies reporting acute corneal allograft rejection following SARS-CoV-2 vaccination; study protocol was developed in line with PRISMA statement. We analysed demographics, allograft type, rejection prophylaxis regime at the time of vaccination, transplantation-to-vaccination time (G-Vt), vaccination-to-immune reaction onset time (V-Rt), management, best-corrected visual acuity before and after rejection, and graft survival. Of 169 titles/abstracts screened, 16 studies (n = 36 eyes) met the inclusion criteria. Fourteen eyes (38.9%) had received >1 graft, and 11.1% of cases had history of immune reactions; 52.9% of cases occurred after the first dose. Median (P25-P75) G-Vt was 48 (10–78) months; median V-Rt was 9 (7–14) days. In eyes with resolved rejection, median time-to-resolution was 3 (1–4) weeks. Four eyes (11.1%) had partial resolution of corneal decompensation, and 5 grafts (13.9%) failed. Acute corneal allograft rejection after SARS-CoV-2 vaccination is a rare event, but may occur any time post-keratoplasty. Early recognition and prompt, aggressive treatment is warranted to optimize vision and graft survival. Well-known risk factors for rejection may be confounding factors, including the high proportion of cases with a history of previous grafts and the rejection prophylaxis regimes at the time of vaccination. Increasing immunosuppressants in the peri-vaccination period may decrease the risk of immune reactions, especially in high-risk cases.

KEYWORDS
coronavirus, keratoplasty, rejection, vaccines

1 | INTRODUCTION

Coronavirus disease (COVID-19), the ongoing pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is still a major public health challenge. The rapid development of a number of vaccines for SARS-CoV-2 was crucial for the prevention of severe manifestations of the disease and death due to COVID-19. SARS-CoV-2 has the potential to affect many tissues and systems, including ocular tissues and adnexa. (Cunha et al., 2020; Lin et al., 2021) The watchful control of adverse events (AEs) of the novel vaccines also led to the detection of rare ocular AEs after SARS-CoV-2 vaccination affecting any ocular structure and the optic nerve. (Y. K. Lee & Huang, 2021; Khan et al., 2021; Ng et al., 2022; Ng et al., 2021) Vaccination-induced corneal allograft rejection episodes have been anecdotally reported after vaccines against other infectious agents (E. H. Lee & Li, 2021) and recently reported after COVID-19 vaccination.

The purpose of this systematic review was to examine all the documented cases of acute corneal allograft rejection following SARS-CoV-2 vaccination, and to characterize possible risk factors and graft outcomes after rejection.

2 | MATERIALS AND METHODS

2.1 | Setting

IMO Grupo Miranza Andorra, IMO Grupo Miranza Barcelona, NOVA Medical School | Faculdade de Ciências Médicas–Universidade Nova de Lisboa (NMS|FCM–UNL).

2.2 | Registration and search strategy

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive electronic database search was done in four databases (PubMed, Cochrane Central Register of Controlled Trials [CENTRAL], Google Scholar, and ClinicalTrials.gov). Hand-search was also performed in reference lists of articles. The search strategy was meant to identify all studies reporting outcomes of acute corneal allograft rejection following SARS-CoV-2 vaccination, and was last run on March 1st, 2022.

2.3 | Eligibility criteria

Eligible studies included patients of any demographic who had acute corneal allograft rejection following SARS-CoV-2 vaccination, and analysed the resolution of the rejection episode after management. We included patients undergoing limbal and/or corneal transplantation.

Articles were included when the original research was published in English, and when at least 1 measurement at the time of diagnosed allograft rejection and 1 measurement after treatment of allograft rejection were reported.

Exclusion criteria were the following: (1) unpublished trials; (2) non-human studies or in vitro studies; (3) non-original studies; (4) publication languages other than English; (5) not full-text article; (6) absence of information of graft outcomes after management of the acute allograft rejection episode; (7) narrative or systematic reviews.

2.4 | Data management and collection

Two reviewers (NM-C, RP-V) independently screened the studies for eligibility, evaluated the quality and extracted the data according to PRISMA guidelines. Accuracy was confirmed by a third reviewer (JLG). Titles and abstracts were screened for inclusion criteria, and full-text articles were retrieved for all the references that met these criteria (Figure 1). Disagreements between reviewers were resolved by deliberation and consensus, and if needed, included an impartial third reviewer (JLG). Efforts to contact authors for further data were made whenever necessary.

Data were extracted from eligible studies according to PRISMA guidelines. Using forms with fields for the following: study first author, year of publication, journal of publication, study design, number of eyes and number of patients, baseline demographics, eligibility criteria, type of corneal and/or limbal allograft, time between corneal transplantation and SARS-CoV-2 vaccination (G-Vt), type of SARS-CoV-2 vaccine administered, number of SARS-CoV-2 vaccine doses received prior to the corneal allograft rejection episode, time between SARS-CoV-2 vaccination and corneal allograft rejection (V-Rt), potential confounding factors reported (including history of previous grafts, high-risk factors for corneal graft rejection, and immunosuppressive therapy at the time of SARS-CoV-2 vaccination) (Dua & Azuara-Blanco, 1999) management strategies for acute corneal allograft rejection, best-corrected visual acuity (BCVA) before SARS-CoV-2 vaccination, at the diagnosis of allograft rejection, and after resolution of the rejection, and corneal clearance after the rejection episode.

2.5 | Quality assessment

Studies were assessed for quality using the Quality Rating Scheme for Studies and Other Evidence ("JAMA Network Open—Instructions for Authors: Ratings of the Quality of the Vidence, n.d.") and by the BMJ Evidence-Based Medicine Tool for evaluating the methodological quality of case reports and case series proposed by Murad et al. (Murad et al., 2018) This is a tool that converged the previous criteria from Pierson, Bradford Hills and Newcastle Ottawa scale modifications into eight items that can be categorized into four domains (selection, ascertainment, causality, and reporting); the assessment of methodological quality was performed qualitatively, as proposed by Murad et al. (Murad et al., 2018). In the interest of simplification, we defined five qualitative categories (very good, good, average, poor, or very poor).

2.6 | Definition of outcomes

Our primary outcome was resolution of corneal graft rejection after treatment. We considered resolution of rejection as resolution of graft rejection signs following treatment as reported by the studies' authors (anatomical resolution) and/or as an improvement in BCVA following resolution of signs of rejection to at least 50% of the value of BCVA reported before the rejection episode (functional resolution). Additional outcomes were the following: final BCVA after corneal allograft rejection, central corneal thickness after allograft rejection, and graft survival after rejection.

3 | RESULTS

3.1 | Search results

Database search identified 195 records, resulting in 169 studies after duplicates were removed. Initial screening through title and abstract excluded 152

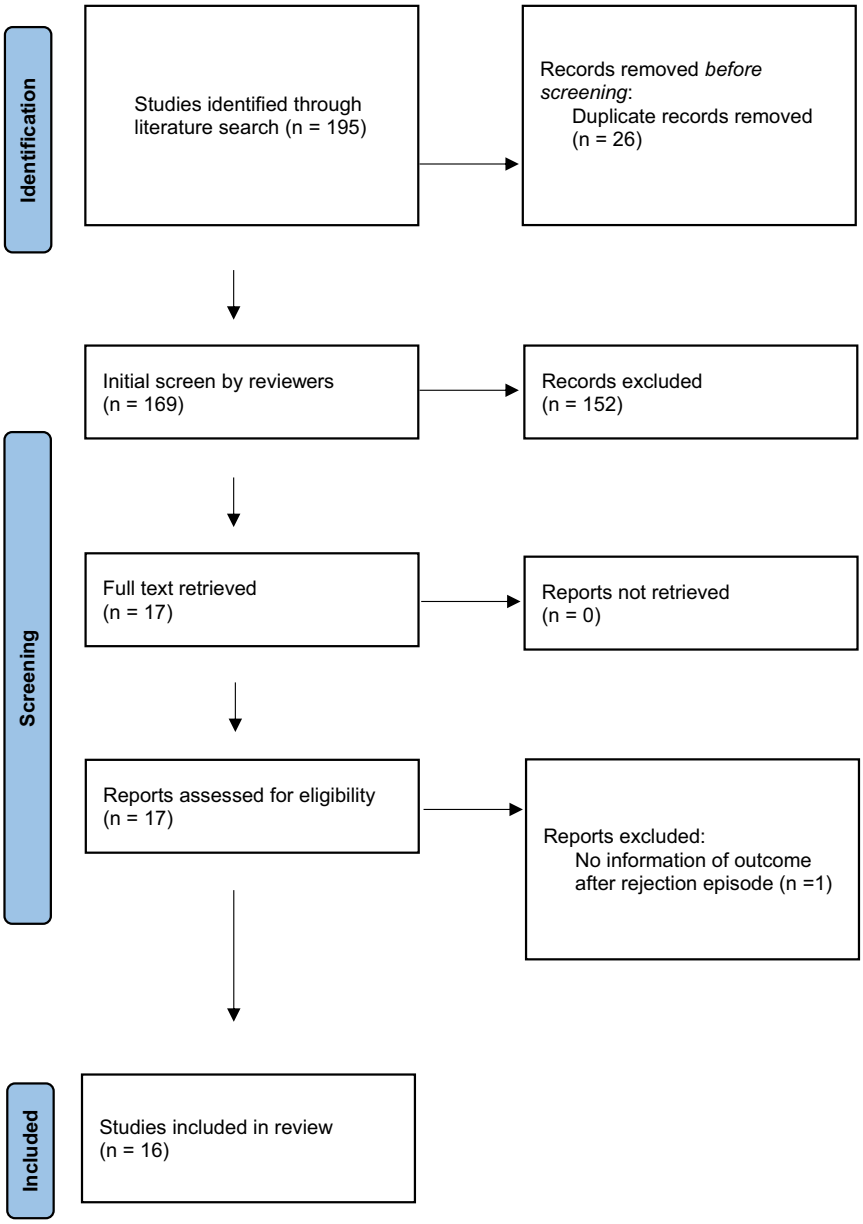

FIGURE 1 Preferred reported items for systematic reviews and meta-analyses (PRISMA) study flow diagram.

studies, leaving 17 papers for full-text assessment (Table S1). The case report by Ravichandran et al. (Ravichandran & Natarajan, 2021) was excluded, since it only presented information at the moment of diagnosis of acute corneal allograft rejection, without mentioning anatomical or functional outcomes after treatment, and so 16 studies were included in the review (Table 1). The PRISMA study flow diagram is presented in Figure 1.

Using the Quality Rating Scheme for Studies and Other Evidence ("JAMA Network Open—Instructions for Authors: Ratings of the Quality of the Vidence, n.d.), all studies received a rating of 4 or 5 (Table S2). Quality data analysis using the BMJ Evidence-Based Medicine Tool for evaluating the methodological quality of case reports and case series found that all studies analysed had at least "average" overall quality (Murad et al., 2018). All studies satisfied the selection domain (item 1), and the exposure was appropriately ascertained in all studies (item 2). All studies reported anatomical outcomes after acute corneal allograft rejection following SARS-CoV-2 vaccination (item 3 "was the outcome adequately ascertained?"), but the studies by Balidis et al., Fujimoto et al., and Gouvea et al. (Balidis et al., 2021; Fujimoto & Kiryu, 2021; Gouvea et al., 2022) did not report the visual outcomes (final BCVA), and the studies by Rajagopal et al. and Abousy et al. (Abousy et al., 2021; Rajagopal & Priyanka, 2022) did not report BCVA before the acute allograft rejection episode. Causality (item 4 alternative causes) was satisfactorily addressed in all studies, although the studies by Rajagopal et al., Balidis et al., Abousy et al., and Gouvea et al. (Abousy et al., 2021; Balidis et al., 2021; Gouvea et al., 2022; Rajagopal & Priyanka, 2022) failed to report the immune rejection prophylaxis regimes in some of their cases. Items 5 ("was there a challenge/rechallenge phenomenon?") and 6 (dose–response effect) of the tool were not included, as they did not apply to the studies analysed. All the cases had sufficient follow-up for outcomes to

TABLE 1 Studies included in the systematic review analysis of acute allograft rejection following SARS-CoV-2 vaccination

Author	Journal	Year	Type of publication	Eyes (*n*)	Patient (*n*)	Eyes (patients)
de la Presa	Cornea	2022	Case report	1	1	1 (1)
Yu	Cornea	2022	Case report	1	1	1 (1)
Shah	Cornea	2022	Case series	4	4	4 (4)
Molero-Senosiain	Cornea	2022	Case series	5	5	5 (5)
Gouvea	Cornea	2022	Case report	1	1	1
Simão	Cornea	2021	Case report	1	1	1 (1)
Rajagopal	IJO	2021	Case report	1	1	1 (1)
Parmar	IJO	2021	Case report	1	1	1 (1)
Balidis	EJO	2021	Case series	4	4	4 (4)
Nioi	Vaccines	2021	Case report	1	1	1 (1)
Abousy	Eye Contact Lens	2021	Case report	2	1	2 (1)
Fujimoto	J Ophthalm Res	2021	Case series	7	7	7 (7)
Wasser	Cornea	2021	Case report	2	2	2 (2)
Rallis	Eye Contact Lens	2021	Brief communication	1	1	1 (1)
Crnej	J Fr Ophthalmol	2021	Letter to the editor	1	1	1 (1)
Phylactou	Br J Ophthalmol	2021	Case series	3	2	3 (2)

occur (item 7), and all studies satisfied the reporting domain (item 8).

3.2 | Baseline demographics

A total of 36 eyes of 34 patients (46% females, mean age 65.1 ± 15.5 years) were included in this analysis (Table 2). Of these, 20 eyes (55.6%) had penetrating keratoplasty (PKP) graft rejection, 13 eyes (36.1%) had endothelial keratoplasty (EK) graft rejection (of which 6 were DMEK eyes and 7 were DSEK/DSAEK eyes), and 3 eyes (8.3%) had a rejection of limbal allografts (of which one was a case with combined PKP plus limbal stem cell transplant, one was an eye with primary keratolimbal allograft [KLAL] and subsequent PKP, and the other had a primary living-related conjunctival-limbal allograft); no cases of acute corneal allograft rejection following SARS-CoV-2 vaccination in eyes with anterior lamellar keratoplasty grafts were found in this analysis.

Fourteen eyes (38.9%) had received at least one previous allograft (Balidis et al., 2021; Dhillon et al., 2017; Gouvea et al., 2022; Molero-Senosiain et al., 2022; Parmar et al., 2021; Phylactou et al., 2021; Rajagopal & Priyanka, 2022; Rallis et al., 2021; Shah et al., 2022; Simão & Kwitko, 2022; Wasser et al., 2021; Yu et al., 2022) including redo PKP (6 eyes), (Balidis et al., 2021; Parmar et al., 2021; Simão & Kwitko, 2022; Wasser et al., 2021; Yu et al., 2022) PKP after limbal or sclerokeratoplasty grafts (2 eyes), (Gouvea et al., 2022; Shah et al., 2022) redo EK (4 eyes), (Balidis et al., 2021; Molero-Senosiain et al., 2022; Phylactou et al., 2021) and PKP after failed EK (2 eyes). (Rajagopal & Priyanka, 2022; Rallis et al., 2021) Two eyes had more than 3 corneal grafts (Molero-Senosiain et al., 2022; Simão & Kwitko, 2022) and four eyes (11.1%) had a history of previous rejection episodes (Abousy et al., 2021; Balidis et al., 2021; Molero-Senosiain et al., 2022; Simão & Kwitko, 2022).

3.3 | Rejection episode after SARS-CoV-2 vaccination

Median (P25-P75) G-Vt was 48 (10–78) months, ranging from 2 weeks (Phylactou et al., 2021) to 25 years after the transplant (Nioi et al., 2021). Immune suppressant regime information at the time of vaccination was reported in 29 eyes, six of which (20.7%) were off topical immunosuppressants; one eye that developed a rejection of a primary KLAL was in subtherapeutic doses of systemic tacrolimus (Gouvea et al., 2022). Eighteen cases (52.9%) of allograft rejection occurred after the first dose of the vaccine, and the remainder after the second dose. The type of vaccine was mRNA in 27 patients (79.4%), of which 19 cases were BNT162b2 vaccine (BioNTech, Pfizer), and 8 cases were mRNA-1273 vaccine (Moderna, NIAID). The type of vaccine was the non-replicating viral vector vaccine in 7 patients (21.6%), of which 4 had received the AZD1222 vaccine (ChAdOx1 nCoV-19, AstraZeneca), 1 had received the CoronaVac (Sinovac), and 2 had received the COVISHIELD™ ChAdOx1 nCoV-19 vaccine.

3.4 | Primary outcome

Resolution of rejection signs on the allograft (anatomical resolution) was reported in 28 eyes (77.8%), with five eyes (13.9%) evolving to allograft failure and three eyes (8.3%) showing partial anatomical improvement. When functional resolution was considered (based on improvement of BCVA to at least 50% of the BCVA before the acute allograft rejection episode), the rate of partial resolution increased to 11.1% due to one case reported by Molero-Senosiain et al. in which BCVA before rejection was 0.52 logMAR and final BCVA after anatomical resolution was 0.80 logMAR (Molero-Senosiain et al., 2022). Management strategies and outcomes of acute corneal

allograft rejection following SARS-CoV-2 vaccination are presented in Tables 3 and 4.

3.5 | Subgroup analysis

When analysis was performed for type of allograft (Tables 3 and 4), five out of 6 DMEK eyes (83.3%) had anatomical and functional resolution, with one case (16.7%) having only partial resolution of the corneal oedema (Balidis et al., 2021); five out of 7 DSEK/DSAEK grafts (71.4%) had anatomical and functional resolution, with one case (14.3%) of only partial resolution of the corneal oedema (Abousy et al., 2021) and one case (14.3%) (which was a redo DSAEK eye) evolving to DSAEK failure (Balidis et al., 2021).

About 15 out of the 20 PKP eyes (75%) had anatomical and functional resolution, with four eyes (20%) evolving to graft failure (Balidis et al., 2021; Fujimoto & Kiryu, 2021; Yu et al., 2022) and one eye (5%) with only partial resolution of the corneal oedema (Balidis et al., 2021). All cases of limbal allograft rejection resolved.

Of note, of the five eyes that evolved to graft failure after the acute rejection episode, three eyes were PKP grafts with a history of previous grafts (one eye was a redo PKP after a large diameter corneal graft (Yu et al., 2022), one was a tertiary PKP graft with history of rejection of the previous graft (Simão & Kwitko, 2022), and the other was a redo PKP (Balidis et al., 2021). The fourth eye was a redo DSAEK, and the fifth case was an eye that underwent primary PKP for herpetic endotheliitis without antiviral prophylaxis at the time of rejection (Fujimoto & Kiryu, 2021).

3.6 | Secondary outcomes

Median (P25-P75) V-Rt was 9 (7–14) days. Median (P25-P75) BCVA decreased from 0.30 (0.10–0.45) logMAR at the last observation before the rejection episode to 0.74 (0.48–1.68) logMAR at the moment of diagnosis of allograft rejection. Management strategies included starting topical corticosteroids (CS) or increasing the frequency of topical CS in all cases. The most frequently prescribed topical CS was dexamethasone 0.1% (13 cases), followed by prednisolone acetate 1% (6 cases), betamethasone 0.1% (4 cases), and difluprednate 0.05% (3 cases); the type of topical CS was not described in 7 cases (Molero-Senosiain et al., 2022; Phylactou et al., 2021; Rajagopal & Priyanka, 2022; Yu et al., 2022). Some corneal surgeons also added oral CS (de la Presa et al., 2022; Fujimoto & Kiryu, 2021; Molero-Senosiain et al., 2022; Parmar et al., 2021; Rajagopal & Priyanka, 2022; Wasser et al., 2021) and/or subconjunctival or intracameral CS to the treatment regime (Balidis et al., 2021). The eye with rejection of the KLAL graft was treated by increasing systemic tacrolimus to a therapeutic dosage.[14]

Median (P25-P75) corneal thickness at the time of acute allograft rejection was 716.5 (609.3–729.0) μm (Balidis et al., 2021; Fujimoto & Kiryu, 2021; Nioi et al., 2021; Phylactou et al., 2021; Rallis et al., 2021; Shah et al., 2022; Simão & Kwitko, 2022) and after resolution of the rejection, it improved to 610 (562.0–655.0) μm. (Balidis et al., 2021; Crnej et al., 2021; Nioi et al., 2021; Phylactou et al., 2021; Rallis et al., 2021; Shah et al., 2022) In eyes with resolved rejection, the median (P25-P75) time-to-resolution was 3 (1–4) weeks.

4 | DISCUSSION

This review of the available reports has found that acute corneal allograft rejection after SARS-CoV-2 vaccination is a rare event, considering the mass vaccination strategy adopted worldwide to achieve the so-called "herd immunity". A global database of COVID-19 vaccinations showed that by March 1, 2022, over 4 billion people had received the complete initial COVID-19 vaccination protocol worldwide, representing 9.39 billion doses (Mathieu et al., 2021). The current estimated prevalence of acute corneal allograft rejection following SARS-CoV-2 vaccination (calculated by dividing the number of events reported until March 1, 2022, by the number of doses administered up to March 1, 2022) would be 0.004 per million doses, which is 10 times lower than previously reported by Wang et al. (Wang et al., 2022) The association between SARS-CoV-2 vaccination and acute corneal allograft rejection episodes is inferred in the published reports by the temporal association, and by the evidence of previous reports of acute rejection episodes following vaccination for other infectious agents (Lee & Li, 2021; Solomon & Frucht-Pery, 1996; Steinemann et al., 1988; Vignapiano et al., 2021; Wertheim et al., 2006; Matoba, 2022); however, these cases are anecdotal, and no statistical association has been proven between vaccination and corneal allograft immune reactions. It has been suggested that vaccinations may trigger inflammatory responses through the development of cross-reactivity with cellular antigens or because of a non-specific immune activation (Lockington, 2021). Proposed mechanisms for acute corneal allograft rejection following SARS-CoV-2 vaccination include the activation of toll-like receptors on the ocular surface and CD4+ T helper-1 cell (Th1) immunity (Ng et al., 2022), and the reduction of the corneal immune privilege due to systemic immune dysregulation (Steinemann et al., 1988). While this mechanism has been better characterized for PKP, it has been less precisely described for EK grafts (Hos et al., 2019); it has been proposed that innate cellular responses or non-cellular rejection mechanisms independent of this classic Th1 mechanisms involved in PKP rejection may be relevant in EK endothelial cell loss and rejection (Luznik et al., 2019).

The analysis of the reported cases of acute corneal allograft rejection following SARS-CoV-2 vaccination shows that a high proportion of eyes had some risk factors for allograft rejection, with approximately 40% of eyes having a history of previous corneal grafts, approximately 11% of eyes having a history of rejection episodes, and nearly 20% of eyes being off any topical immunosuppressants at the time of vaccination. The Collaborative Corneal Transplantation Studies reported an additional 15% of immune reaction episodes (rejection episodes) for

TABLE 2 Baseline demographics and SARS-CoV-2 vaccination data

Author	Eyes (patients)	Gender/age (years)	Race	Transplant	History of previous graft
de la Presa	1 (1)	F/27	N/R	Primary LR-CLAL	No
Yu	1 (1)	M/51	N/R	Redo PKP, large diameter graft	Yes
Shah	4 (4)	M/74	Caucasian	Unilateral DMEK	No
		F/61	Caucasian	Unilateral sclerokeratoplasty + PKP	Yes
		F/69	African American	DSAEK	No
		M/77	Caucasian	PKP	No
Molero-Senosiain	5 (5)	F/72	Caucasian	Redo DSAEK (third graft)	Yes
		F/82	Caucasian	Primary DSAEK	No
		M/55	Asian	Primary PKP	No
		M/61	Caucasian	Primary PKP	No
		F/48	Caucasian	Primary PKP	No
Gouvea	1	M/72	N/R	Primary KLAL + subsequent PKP	Yes
Simão	1 (1)	F/63	Asian	Redo PKP (third graft)	Yes
Rajagopal	1 (1)	M/79	N/R	PKP after failed DSEK	Yes
Parmar	1 (1)	M/35	Indian	Redo PKP	Yes
Balidis	4 (4)	F/77	Caucasian	Redo DMEK	Yes
		F/63	Caucasian	Redo PKP	Yes
		M/69	Caucasian	Primary PKP	No
		M/63	Caucasian	Redo DSAEK	Yes
Nioi	1 (1)	F/44	Caucasian	Primary PKP	No
Abousy	2 (1)	F/73	N/R	Primary DSEK	No
				Primary DSEK	No
Fujimoto	7 (7)	M/80	N/R	Primary PKP	No
		F/32	N/R	PKP+LSCT	No
		M/50	N/R	Primary PKP	No
		M/55	N/R	Primary PKP	No
		F/92	N/R	Primary PKP	No
		M/87	N/R	Primary PKP	No
		M/84	N/R	Primary DSAEK	No
Wasser	2 (2)	M/73	N/R	Redo PKP	Yes
		M/56	N/R	Redo PKP	Yes
Rallis	1 (1)	F/68	N/R	PKP after failed DSAEK	Yes
Crnej	1 (1)	M/71	N/R	Primary DMEK	No
Phylactou	3 (2)	F/66	Caucasian	Primary DMEK	No
		F/83	Caucasian	Primary DMEK	No
				DMEK after failed DSAEK	Yes

Abbreviations: COVISHIELD, ChAdOx1nCoV-19 Corona Virus Vaccine Recombinant COVISHIELD; CsA, cyclosporine A; Dexa, dexamethasone; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; F, female; FML, fluorometholone; G-Vt, time between graft and vaccination; KLAL, keratolimbal allograft; LR-CLAL, living-related conjunctival-limbal allograft; LSCT, limbal stem cell transplantation; M, male; MMF, mycophenolate mofetil; N/R, not reported; PDN, prednisolone; PKP, penetrating keratoplasty; V-Rt, time between vaccination and immune reaction episode.

History of immune reaction episodes	G-Vt (months)	Immunosuppressants at the time of vaccination	SARS-CoV-2 vaccine	Doses (*n*)	V-rt (days)
No	55	MMF 500 mg day + PDN 1% 2id	Moderna	1	15
No	0.75	Topical CS 4id	Moderna	1	3
No	5	Topical FML 0.1% 1id	Moderna	1	7
No	30	PDN 1% 1id	Moderna	2	7
No	72	PDN 1% 1id	Moderna	2	14
No	264	Inconsistent use of topical steroids	Moderna	2	7
No	48	Dexa 0.1% 4id	Pfizer	1	14
No	48	Off steroids 2 years before vaccination	Pfizer	1	14
No	104	0	AZD1222	2	7
No	240	N/R	AZD1222	2	28
Yes	48	Dexa 0.1% 1id	Pfizer	1	28
No	78	Systemic Tacrolimus subtherapeutic	Pfizer	2	30
Yes	84	0.03% Tacrolimus, off steroids 2 years before vaccination	CoronaVac	1	1
No	48	0	COVISHIELD	2	42
No	6	PDN 1% 1id + CsA 0.05% 2id	COVISHIELD	1	4
Yes	12	Dexa 0.1% + oral valacyclovir	Moderna	1	7
No	24	N/R	Moderna	2	7
No	22	N/R	AZD1222	1	5
No	9	Topical Dexa 1id	AZD1222	1	10
No	300	N/R	Pfizer	1	13
Yes	96	N/R	Pfizer	2	4
No	96	N/R			9
No	Mean 687.4 ± 647.5 days (22.9 ± 21.6 months) (range 6.7–68.5 months)	FML 0.1% 4id	Pfizer	2	46 from 1st dose
No		Betamethasone 0.1% 4id + Tacrolimus 0.1% 2id	Pfizer	2	87 from first dose
No		Betamethasone 0.1% 6id + Tacrolimus 0.1% 2id	Pfizer	2	102 from first dose
No		0	Pfizer	1	14
No		Betamethasone 0.1% 4id	Pfizer	2	111 from 1st dose
No		Betamethasone 0.1% 2id	Pfizer	2	82 from 1st dose
No		FML 0.1% 2id	Pfizer	2	41 from 1st dose
No	24	Dexa 0.1% 1id	Pfizer	1	13
No	10	Off steroids 4 months before vaccination	Pfizer	1	14
No	4	PDN 0.5% 4id	Pfizer	1	4
No	5	N/R	Pfizer	1	7
No	0.5	Dexa 0.1% 4id	Pfizer	1	7
No	72	Off steroids 6 months before vaccination	Pfizer	2	21
No	36				

TABLE 3 Management and outcomes of endothelial keratoplasty after acute corneal allograft rejection following SARS-CoV-2 vaccination

Author	Type of EK allograft	Management	Graft outcome	Time-to-resolution (weeks)
Shah	Primary DMEK	Topical PDN 1% q2h	Resolution of acute rejection episode	5
	Primary DSAEK	Topical Difluprednate 0.05% 6id	Resolution of acute rejection episode	3
Molero-Senosiain	Redo DSAEK (third graft)	Topical Dexa 0.1% q1H	Resolution of acute rejection episode	3
	Primary DSAEK	Intensive topical CS non-specified	Resolution of acute rejection episode	3
Balidis	Redo DMEK	Subconjunctival Dexa + topical Dexa 0.1% q2h	Worsening requiring IV CS and topical Dexa 0.1% q1h, started improvement at 4 weeks	Partial resolution
	Redo DSAEK	Topical Dexa q2h + hypertonic ointment	Failed DSAEK graft	Failed
Abousy	Primary DSEK	Topical PDN 1% 4id	At 4 weeks required topical PDN 1% q1h + ointment (20/80). Partial resolution of corneal oedema	Partial improvement
	Primary DSEK	Topical PDN 1% 4id	At 4 weeks required topical PDN 1% q1h + ointment (20/150). Resolution of acute rejection episode	8
Fujimoto	Primary DSAEK	Topical Betamethasone 0.1% 4id + Tacrolimus 0.1% 2id	Resolution of acute rejection episode	N/R
Crnej	Primary DMEK	Topical Dexa 0.1% q2h + Oral valacyclovir 1 g q8h	Resolution of acute rejection episode	1
Phylactou	Primary DMEK	Topical Dexa 0.1% q1h	Resolution of acute rejection episode	1
	Primary DMEK	Topical CS q1h	Resolution of acute rejection episode	1
	DMEK after failed DSAEK	Topical CS q1h	Resolution of acute rejection episode	1

Abbreviations: BCVA, best-corrected visual acuity; CS, corticosteroid; Dexa, dexamethasone; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; EK, endothelial keratoplasty; IV, intravenous; MPDN, methylprednisolone; N/A, not applicable; N/R, not reported; PDN, prednisolone.

each additional PKP graft (Maguire et al., 1994). These are potentially confounding factors in the interpretation of the relationship between association, correlation, and causation.

Importantly, reported immune reactions after COVID-19 vaccination occurred at any time after keratoplasty, anywhere from 14 days to 25 years after surgery. Management strategies for the prevention of acute rejection episodes after vaccination are not consensual amongst corneal surgeons, and nearly half of corneal specialists do not alter management in the setting of keratoplasty and vaccinations. However, there is an overall attitude towards increasing topical CS in the peri-vaccination period, particularly in patients with recent EK surgery, and towards topical CS coverage in high-risk PKP scenarios (Lockington et al., 2021). We believe that increasing immunosuppressant prophylaxis in the vaccination period may decrease the risk of acute rejection episodes, especially in high-risk cases (Moura-Coelho et al., 2021). All patients with corneal allografts should be regularly reminded of the clinical symptoms of rejection and advised to seek urgent review to start treatment promptly (Lockington, 2021); in our clinical practice, the patients are taught the mnemonic "RSVP" for redness, sensitivity to light, vision blurring, and pain. (Moura-Coelho et al., 2021). We also remind general ophthalmologists that any inflammation in an eye with a prior corneal graft should be suspected of being graft rejection until proven otherwise.

A larger number of cases of acute corneal allograft rejection following SARS-CoV-2 vaccination were treated with topical dexamethasone, compared with the number of patients that were treated with topical prednisolone. These findings contrast slightly to the practice patterns previously reported by Kharod-Dholakia et al. (Kharod-Dholakia et al., 2015), where prednisolone was reported as the drug of choice for the management of allograft rejection.

While the prognosis for BCVA and for graft survival were good overall, 25% of the PKP eyes with acute corneal allograft rejection following SARS-CoV-2 vaccination had incomplete resolution or graft failure, and although the risk of graft failure due to rejection after EK is relatively low (Price et al., 2018; Stulting et al., 2018) as many as 20–25% of EK eyes may be at risk of decreased corneal transparency or graft failure due to immune reaction after SARS-CoV-2 vaccination.

BCVA at last observation before immune reaction (logMAR)	BCVA at diagnosis of immune reaction (logMAR)	Final BCVA (logMAR)	Corneal thickness before immune reaction (µm)	Corneal thickness at immune reaction (µm)	Final corneal thickness (µm)
0.10	0.48	0.30	N/R	743	655
0.10	0.40	0.20	N/R	719	633
0.42	0.60	0.48	N/R	N/R	N/R
0.3	0.70	0.50	N/R	N/R	N/R
N/R	N/R	N/R	N/R	720	710
0.30	1.9	N/A (failed graft)	N/R	N/R	N/R
N/R	0.54	0.40	N/R	N/R	N/R
N/R	0.3	0.10	N/R	N/R	N/R
0.22	0.3	N/R	641	724	N/R
0.18	0.8	0.10	N/R	714	512
0.00	0.78	0.00	525	652	526
0.00	0.60	0.00	N/R	N/R	N/R
0.00	0.30	0.00	N/R	N/R	N/R

The main strengths of our study are: (1) Our database search enabled us to find the largest number of reported cases (more than the previous summary of evidence), (Wang et al., 2022) and is the only study summarizing evidence including published data in 2022, being the most up to date database search available; and (2) we provide an in-depth analysis of potentially confounding factors and of the clinical outcomes of acute corneal allograft rejection following SARS-CoV-2 vaccination. The main limitation of this review is the fact that only case reports or small case series were found in the literature search. Another important limitation is that the number of publications on acute rejection after SARS-CoV-2 vaccination exceeds by far the number of reports of keratoplasty patients developing corneal allograft rejection after other vaccines; while this is possibly due to increased awareness of the potential of immunization-induced immune reactions on corneal grafts, it is also possible that the novelty of the viral agent and the novelty of the mRNA vaccines raised a potential publication bias. We emphasize our belief that the benefits of SARS-CoV-2 vaccination far outweigh the potential risks of acute corneal allograft rejection following vaccination, considering the potentially severe complications of COVID-19 disease, and considering the potential ocular manifestations of COVID-19 (Cunha et al., 2020), which may also include acute corneal graft rejection (Ang et al., 2020; Behera et al., 2021; Jin & Juthani, 2020; Singh & Mathur, 2021). Most corneal surgeons agree with this policy, according to a recent survey of 142 corneal surgeons (Lockington et al., 2021).

In conclusion, acute corneal allograft rejection following SARS-CoV-2 vaccination is a rare event, but may occur at any time post-transplantation and may threaten vision and graft survival. Well-known risk factors for allograft rejection may be confounding factors for post-vaccination immune reactions. Early recognition of symptoms and signs of acute rejection and prompt, aggressive treatment is warranted to optimize vision and graft survival. Increasing immunosuppressants in the peri-vaccination period may decrease the risk of acute rejection episodes, especially in high-risk cases.

TABLE 4 Management and outcomes of penetrating keratoplasty grafts and limbal allografts after acute corneal allograft rejection following SARS-CoV-2 vaccination

Author	Transplant	Management	Graft outcome	Time-to-resolution (weeks)
de la Presa	Primary LR-CLAL	Difluprednate 0.05% q1h + PDN 30 mg day	Resolution of acute rejection episode	4
Yu	Redo PKP, large diameter graft	Topical CS q2H	Graft failure	N/A (failed graft)
Shah	Unilateral sclerokeratoplasty + PKP	Topical PDN 1% q1h	Resolution of acute rejection episode	6
	PKP	Topical PDN 1% 5id	Resolution of acute rejection episode	1
Molero-Senosiain	Primary PKP	Intensive topical CS non-specified	Resolution of acute rejection episode	3
	Primary PKP	Intensive topical CS non-specified + IV MPDN 3 pulses 500 mg q48h	Resolution of acute rejection episode	2
	Primary PKP	Topical Dexa 0.1% q1H	Resolution of acute rejection episode	1
Gouvea	Primary KLAL + subsequent PKP	Topical Difluprednate 0.05% q1H + Increased Systemic tacrolimus 2 mg 2id	Resolution of acute rejection episode	16
Simão	Redo PKP (third graft)	Topical Dexa q1H + polydimethylsiloxane 4id + timolol + bimatoprost	Partial resolution, recurrence 1 month after (2nd dose of vaccine) leading to graft failure	N/A (failed graft)
Rajagopal	PKP after failed DSEK	Topical CS q1h + Oral CS	Resolution of corneal oedema, with mild residual stromal haze	8
Parmar	Redo PKP	Topical PDN 1% q1H + atropine 1% 3id + intravenous MPDN bolus 3 days 3 g then oral PDN 60 mg/day	Resolution of acute rejection episode	3
Balidis	Redo PKP	Topical CS q1h + Intracameral CS	Unresolved corneal oedema	N/A (failed graft)
	Primary PKP	Topical CS + Oral CS + Subconjunctival dexa	Partial resolution	Partial improvement
Nioi	Primary PKP	Topical Dexa 0.2% q1h + cholecalciferol 1000 IU daily	Recurrence at 8-week, resolved with reintroduction of topical steroids	4
Fujimoto	Primary PKP	Topical Betamethasone 0.1% 6id + Acyclovir ointment 5id	Graft failure	N/A (failed graft)
	PKP + LSCT	Topical FML 0.1% q1H	Resolution of acute rejection episode	N/R
	Primary PKP	Add oral PDN 20 mg/day	Resolution of acute rejection episode	N/R
	Primary PKP	Topical FML 0.1% q1H	Resolution of acute rejection episode	N/R
	Primary PKP	Topical Betamethasone 0.1% 4id	Resolution of acute rejection episode	N/R
	Primary PKP	Topical Betamethasone 0.1% 4id	Resolution of acute rejection episode	N/R
Wasser	Redo PKP	Topical Dexa 0.1% q1h + Oral PDN 60 mg	Resolution of acute rejection episode	1
	Redo PKP	Topical Dexa 0.1% q1h + Oral PDN 60 mg	Resolution of acute rejection episode	2
Rallis	PKP after failed DSAEK	Topical Dexa 0.1% q1h + Oral acyclovir 400 mg 5id	Resolution of acute rejection episode	3

Abbreviations: BCVA, best-corrected visual acuity; CS, corticosteroid; Dexa, dexamethasone; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; IV, intravenous; KLAL, keratolimbal allograft; LR-CLAL, living-related conjunctival-limbal allograft; LSCT, limbal stem cell transplantation; MPDN, methylprednisolone; N/A, not applicable; N/R, not reported; PDN, prednisolone; PKP, penetrating keratoplasty.

BCVA at last observation before immune reaction (logMAR)	BCVA at diagnosis of immune reaction (logMAR)	Final BCVA (logMAR)	Corneal thickness before immune reaction (µm)	Corneal thickness at immune reaction (µm)	Final corneal thickness (µm)
0	0.00	0.00	N/R	N/R	N/R
1.30	2.30	N/A (failed graft)	N/R	N/R	N/R
0.30	0.60	0.48	N/R	752	610
0.10	0.48	0.30	N/R	N/R	N/R
0.52	1.90	0.80	N/R	N/R	N/R
0.7	1.24	0.80	N/R	N/R	N/R
0.36	1.90	0.70	N/R	N/R	N/R
0.54	0.6	N/R	N/R	N/R	N/R
0.40	1.00	N/A (failed graft)	507	841	N/R
N/R	0.78	0.78	N/R	N/R	N/R
0.78	1.80	0.18	N/R	N/R	N/R
0.10	0.80	N/A (failed graft)	470	585	N/R
N/R	N/R	N/R	535	757	660
0.18	1.90	0.18	560	692	562
0.40	1.30	N/A (failed graft)	584	726	N/R
0.04	0.30	N/R	552	649	N/R
2.3	2.4	N/R	493	536	N/R
0	0.48	N/R	512	586	N/R
0.3	0.4	N/R	506	596	N/R
0.3	0.4	N/R	459	561	N/R
0.60	1	0.60	N/R	N/R	N/R
0.10	2	0.10	N/R		N/R
0.48	1.90	0.30	N/R	730	609

AUTHOR CONTRIBUTION

Nuno Moura-Coelho: conceptualization, methodology, research design, writing of the original draft, writing review and editing, data analysis. João Paulo Cunha: data analysis, writing review and editing, supervision, validation. Renato Papa: data analysis, writing of the original draft. Óscar Gris: supervision, validation. José Güell: conceptualization, methodology, research design, writing review and editing, supervision, validation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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