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Adverse Events Associated With SARS-CoV-2 Vaccination in Patients With Glomerular Diseases and the Potential Risk of Disease Reactivation

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Received 12 December 2023; revised 23 July 2024; accepted 5 August 2024; published online 10 August 2024

Kidney Int Rep (2024) **9,** 3324–3327; https://doi.org/10.1016/j.ekir.2024.08.003
KEYWORDS: adverse reactions; glomerular disease; recurrence; SARS-CoV-2; vaccination

INTRODUCTION

Active immunization against SARS-CoV-2 has been a critical mitigation tool during the pandemic.[1,S1,S2] Patients with glomerular diseases (GDs) are at risk for severe illness caused by SARS-CoV-2, due to impaired kidney function and long-standing immunosuppressive therapy. Therefore, vaccination is of high importance for these patients. However, multiple reports have described new onset or relapse of GDs following SARS-CoV-2 vaccination, although details of clinical characteristics of vaccine-associated GD recurrence are unknown.[2,3,S3] In the light of potential vaccine hesitancy, realistic information regarding alterations of GD activity status after vaccination against SARS-CoV-2 is needed, to assist patients and clinicians in reaching the decision to vaccinate.

This study aimed to assess the frequency of adverse events following SARS-CoV-2 vaccination in patients with GDs, including potential impact in kidney indexes, and the probability of disease recurrence (Supplementary Methods).

RESULTS

A total of 315 patients with a history of biopsy-proven GD were included. Most of them (96.2%) had received 3 (3–4) doses of the BNT162b2 vaccine with the median time to first dose being 48.9 months from the diagnostic kidney biopsy (Supplementary Table S1). The proportion of patients experiencing any systemic reaction or local adverse event at the site of administration (myalgias, pain) after vaccination was 21% and 38.7%, respectively, whereas none required hospitalization. The follow-up time was 18.2 (15.5–20.1) months starting from the time of administration of first vaccine dose (Supplementary Table S2).

Activity Status of GD Before and After Vaccination

At vaccination, 224 patients (87.8%) were in GD remission and 31 (12.2%) had active GD. Twenty-three

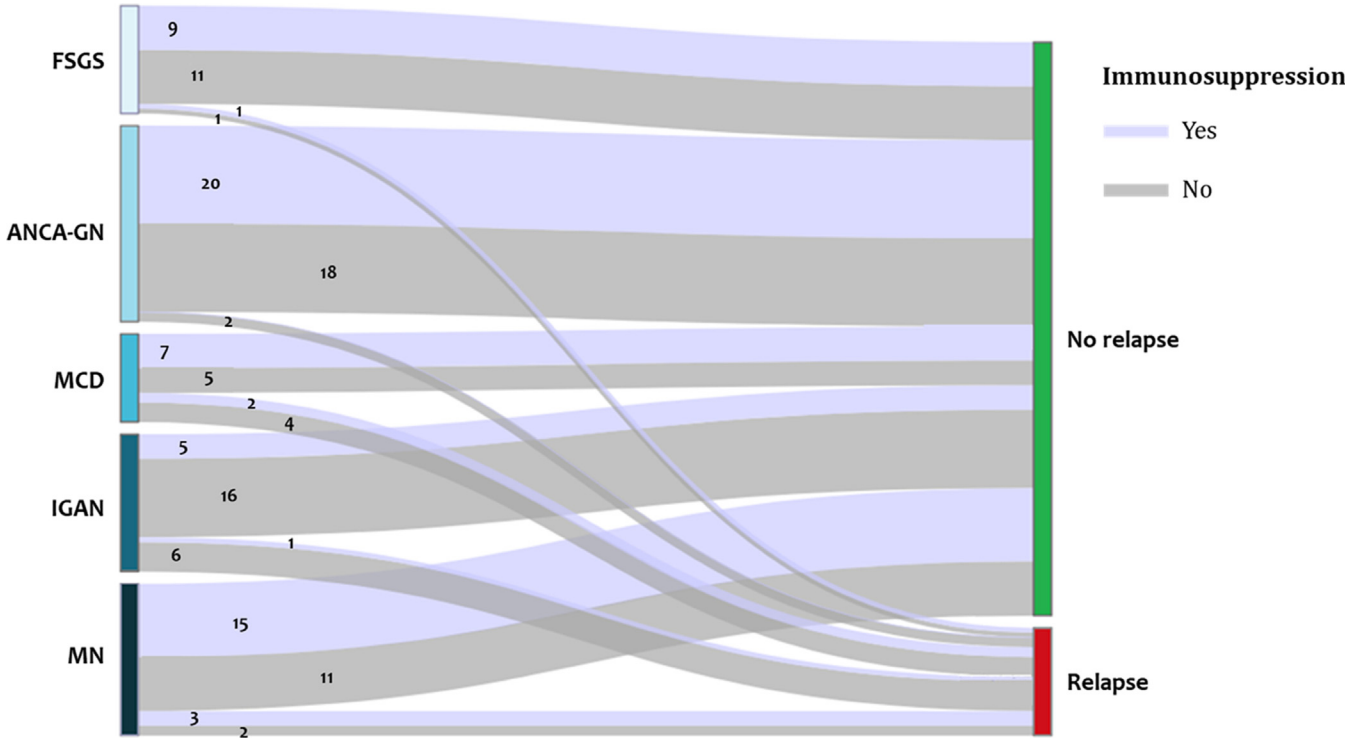

Figure 1. Sankey diagram showing the activity status for each histopathological diagnosis by the presence of ongoing immunosuppressive therapy. ANCA-GN, anti-neutrophil cytoplasmic autoantibodies glomerulonephritis; FSGS, focal segmental glomerulosclerosis; IGAN, IgA nephropathy; MCD, minimal chnage disease; MN, membranous nephropathy.

patients (9%) experienced GD reactivation, that is, relapse, within a median time of 2.5 (1.2–6.4) months from the first dose. In contrast, 10 patients with active GD at vaccination achieved remission by the end of follow-up time (Supplementary Table S3).

Characteristics of Relapses

The mean age at GD diagnosis was 47.9 years and 10 (43.5%) were males. The majority received the BNT162b2 vaccine (at the time of relapse, 1 patient had received 1 vaccine dose, 3 patients had received 2 doses, and 19 patients had received 3 doses) whereas from GD diagnosis to vaccination elapsed 100.8 (± 86.5) months, and 16 patients (69.5%) were off immunosuppressive therapy. Overall, time to relapse was 2.5 (1.2–6.4) months and serum creatinine and estimated glomerular filtration rate[4,S4,S5] values before and after vaccination were similar (1.1 [± 0.39] mg/dl vs. 1.2 [± 0.46] mg/dl, $P = 0.869$) and (72.7 [± 2501] ml/min vs. 66 [± 26.1] ml/min, $P = 0.854$), respectively (Supplementary Table S4). Two of the relapses had antineutrophil cytoplasmic autoantibody-glomerulonephritis, 1 had IgA vasculitis, whereas all others had primary GDs, (6 with minimal change disease [MCD], 5 with membranous nephropathy [MN], and 2 with primary focal segmental glomerulosclerosis) or IgA nephropathy (7 patients) (Figure 1; Table 1). Overall, 73.9% of relapsing patients required reinstitution or upgrade of immunosuppression, including 10 (43.5%) with overt nephrotic syndrome (24-hour proteinuria, 6562 ± 2940 mg). All but 2 patients achieved remission of nephrotic syndrome by the end of follow-up. Seven patients (30.4%) had IgA nephropathy recurrence manifested with new onset of active urine sediment and variable increases in 24-hour proteinuria. At relapse, 7 of 23 patients were on immunosuppression, including 5 on low-dose glucocorticoids (2 also on cyclosporine) whereas 1 patient was on cyclosporine and anakinra, and 1 on mycophenolate mofetil. For GD relapse, 14 of 23 received glucocorticoids and 5 of 19 received combined therapy with glucocorticoids and cyclophosphamide (2 with antineutrophil cytoplasmic autoantibody-glomerulonephritis, 1 with IgA vasculitis, 2 with MN). One patient was lost to follow-up and 3 with IgA nephropathy were managed with no immunosuppressive agents. None experienced renal failure or ended up with end-stage kidney disease during the follow-up time.

The Impact of Immunosuppression

Among vaccinated patients with available data regarding immunosuppressive therapy at vaccination, 111 (79.9%) were in remission and 16 (20.1%) were still active. Experience of GD relapse following vaccination was more frequent among patients who were off immunosuppression (18.15%) compared with those on immunosuppression (7.8%) ($P = 0.058$), whereas time

Table 1. Glomerular disease activity status before and after vaccination and characteristics of the relapses

Parameter, *n* (%)	Vaccinated individuals
GD status at vaccination	$N = 255$
Remission	224 (87.8)
Active	31 (12.2)
GD Relapse after vaccination	23 (9.0)
Histopathological diagnosis of relapse	$N = 23$
ANCA-glomerulonephritis	2 (8.7)
IgA nephropathy	7 (30.4)
Minimal change disease	6 (26.1)
Membranous nephropathy	5 (21.7)
IgA vasculitis	1 (4.3)
Focal segmental glomerulosclerosis	2 (8.7)
Time to relapse from vaccination (mo)	2.5 (1.2–6.4)
GD activity status at end of follow-up	$N = 208$
Remission	198 (95.2)
Active	10 (4.8)
Patients who achieved remission after vaccination (among active patients at vaccination)	10 (32.3)
Follow-up time (mo)	18.2 (15.5–20.1)
Histopathology diagnosis	Frequency of relapses
Minimal change disease ($N = 29$)	6 (20.1)
Focal segmental glomerulosclerosis ($N = 38$)	2 (5.2)
Membranous nephropathy ($N = 63$)	5 (7.9)
IgA nephropathy ($N = 41$)	7 (17.1)
Lupus nephritis ($N = 69$)	0 (0)
Histopathology diagnosis	% (95% CI)
Minimal change disease	20.1 (5.6–34.7)
Focal segmental glomerulosclerosis	5.2 (0–12.2)
Membranous nephropathy	7.9 (1.2–14.6)
IgA nephropathy	17.1 (5.6–28.6)
Lupus nephritis	0
ANCA-glomerulonephritis	3.0 (0–7.1)

ANCA, antineutrophil cytoplasmic autoantibody; CI, confidence interval; GD, glomerular disease.

to relapse was shorter among those on immunosuppressive therapy compared with those off therapy (1.2 vs. 4.2 months [$P = 0.03$]).

DISCUSSION

This study explored the frequency of adverse events associated with vaccination against SARS-CoV-2 in patients with GDs, including the probability of GD reactivation.

Patients with biopsy-proven GD, who received at least 1 dose of the SARS-CoV-2 vaccine and had been diagnosed with GD prior to vaccination were studied retrospectively whereas those who ended up with end-stage kidney disease prior to vaccination or received the diagnosis of GD after vaccination were excluded. The proportion of patients with systemic events in this cohort was 21% without clinical sequalae in most cases. Nine percent of patients experienced recurrence of the GD, leading to reinstitution of immunosuppressive therapy in 73.9%; however, none of them experienced kidney function decline, end-stage kidney disease, or death attributed to recurrence. Patients who experienced an alteration in the activity status from remission to active disease were considered to have a relapse of the GD. Time to relapse counted from the first vaccine dose. Relapses were more frequent among patients, who had discontinued immunosuppressive therapy, after being in long-term sustained remission. Time to relapse was shorter in non-immunosuppressed patients compared to those on immunosuppression, whereas the relapse-free survival did not differ across histopathological diagnoses. BNT162b2 was the most widely used vaccine, which is known for its favorable safety profile.[1] The concern about reactivation of GDs is widely spread in clinicians and patients starting from the first reported case of new-onset MCD after receiving the COVID-19 vaccine.[S6,S7] Several reports have described new-onset or relapse of GDs following COVID-19 vaccination. Teragaki *et al*.[4] reported that 77% of new-onset cases developed MCD after the first dose and 73% were diagnosed within 10 days.

Overall, the most reported GDs are MCD[4,5] and IgA nephropathy[6] as in our cohort. The pathogenesis behind relapses of nephrotic syndrome following SARS-CoV-2 vaccination have been widely attributed to the activation of angiotensin-converting enzyme-2 receptors, leading to podocyte effacement, and/or dysregulation of T cells, cytokine production, and subsequent podocyte injury.[S8-S10]

Nevertheless, relapse or occurrence of GD *de novo*[S10-13] and especially MN following immunization with the inactivated SARS-CoV-2 vaccine has been reported with the nephrotic syndrome entering partial remission after treatment with angiotensin II receptor blocker.[7] A retrospective study of 245 patients with biopsy-proven MN found the relapse rate of nephrotic syndrome being 5% during the SARS-CoV-2 pandemic era, compared to 2% prior to it.[8] Another report showed that the secondary or booster vaccinations enhanced cytokine secretion compared to the first dose.[9]

Limitations of this study include its retrospective design and the fact that included patients were from different centers. However, most of them were university hospitals, ensuring homogeneity of the diagnostic and therapeutic lines. Besides, one might speculate that reactivation of GDs might occur coincidentally following vaccination. However, GDs relapse after influenza or hepatitis B vaccination has not been commonly reported although they have been extensively used for several decades.

Immunosuppressed people living with autoimmune disorders of the kidney are at risk for prolonged SARS-CoV-2 replication, interhost viral evolution of mutated variants, and poor clinical outcomes. This acknowledges the overwhelming benefits of vaccination in

patients with GDs, who face a significant risk of devastating COVID-19 complications, including death, end-stage kidney disease, long-COVID-19 infection, due to chronic kidney disease and immunosuppression, which should be emphasized in our communication with patients to avoid vaccination hesitancy. Our findings indicate only a temporal relationship between reactivation of GDs and SARS-CoV-2 vaccination, mainly supported by the time sequalae and certainly not a causation. Nevertheless, a similar number of relapses might also occur during routine follow-up of these patients without expose in SARS-CoV-2 vaccination. Therefore, further investigation for better understanding of COVID-19–related renal diseases are crucial for effective GD patient management and vaccination efforts in this population.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Table S1. Demographics and glomerular disease associated characteristics of the cohort.

Table S2. Characteristics of the Sars-CoV-2 vaccination and the associated adverse events.

Table S3. Immunosuppressive therapy at vaccination and the risk of relapse.

Table S4. Laboratory measurements before and after vaccination.

STROBE Checklist

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