OXFORD

QJM: An International Journal of Medicine, 2022, 1–14

https://doi.org/10.1093/qjmed/hcac185
Advance Access Publication Date: 3 August 2022
Review

REVIEW

New-onset IgA nephropathy following COVID-19 vaccination

Y. Ma and G. Xu

From the Department of Nephrology, The Second Affiliated Hospital of Nanchang University, No. 1, Minde Road, Donghu District, Nanchang 330006, P.R. China

Address correspondence to Prof. G. Xu, Department of Nephrology, The Second Affiliated Hospital of Nanchang University, No. 1, Minde Road, Donghu District, Nanchang 330006, P.R. China. email: gaosixu@163.com

Abstract

Coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused significant economic and health damage worldwide. Rapid vaccination is one of the key strategies to curb severe illness and death due to SARS-CoV-2 infection. Hundreds of millions of people worldwide have received various COVID-19 vaccines, including mRNA vaccines, inactivated vaccines and adenovirus-vectored vaccines, but the side effects and efficacy of most vaccines have not been extensively studied. Recently, there have been increasing reports of immunoglobulin A nephropathy (IgAN) after COVID-19 vaccination, however, whether their relationship is causal or coincidental remains to be verified. Here, we summarize the latest clinical evidence of IgAN diagnosed by renal biopsy associated with the COVID-19 vaccine published by 10 July 2022 with the largest sample size, and propose a hypothesis for the pathogenesis between them. At the same time, the new opportunity presented by COVID-19 vaccine allows us to explore the mechanism of IgAN recurrence for the first time. Indeed, we recognize that large-scale COVID-19 vaccination has enormous benefits in preventing COVID-19 morbidity and mortality. The purpose of this review is to help guide the clinical assessment and management of IgA nephropathy post-COVID-19 vaccination and to enrich the 'multi-hit' theory of IgA nephropathy.

Introduction

With the ongoing pandemic of coronavirus disease 2019 (COVID-19) and the continuous emergence of new variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it has caused great harm to human health.[1] The most pronounced clinical symptoms in patients with COVID-19 are severe infections due to the fact that SARS-CoV-2 usually attacks the respiratory system first. However, there is a growing evidence that the virus can also affect other organs, and gastrointestinal symptoms and kidney damage are relatively common in this infection and are associated with increased mortality.[2] Rapid and large-scale SARS-CoV-2 vaccination has been one of the key strategies to contain the COVID-19 pandemic. In recent years, hundreds of millions of people around the world have been vaccinated with various COVID-19 vaccines, including mRNA vaccines (Pfizer, Moderna and CureVac), inactivated vaccines (Sinovac Life Science and CoronaVac) and adenovirus vector vaccines (Janssen and Oxford-AstraZeneca). The mRNA vaccine is a novel vaccine consisting of lipid nanoparticles surrounding the mRNA encoding the SARS-CoV-2 spike protein. Once injected, the mRNA is translated into the target protein, resulting in a robust cellular and humoral immune response by generating antigen-specific follicular T cells and germinal center B cells[3] and activated $CD4^+$ and $CD8^+$ T cells.[4] Large clinical trials have shown that vaccination against SARS-CoV-2 has high efficacy and safety in preventing COVID-19 infection. The most common adverse events include injection site tenderness, fever, fatigue, body aches and headaches, and rarely have serious reactions.[5–7]

Received: 11 July 2022

However, with the widespread use of SARS-CoV-2 vaccines around the world, growing number of reports describe the pathogenesis of glomerular diseases, such as immunoglobulin A nephropathy (IgAN), minimal change disease, antineutrophil cytoplasmic antibody-associated vasculitis and so on.[8] Most cases were associated with mRNA vaccines (Pfizer and Moderna) and adenoviral vector delivery.[9–12] Currently, IgAN is the most common glomerular disease after COVID-19 vaccination, which is characterized by mesangial immunodeposits of IgA1 with mesangial proliferation.[13] However, it is unclear whether the COVID-19 vaccine can cause an immune response to trigger IgA antibodies production or form pathogenic IgA and form new immune deposits in the kidneys, or whether the immune response to the vaccine simply reveals pre-existing deposits. In this review, we summarized the most recent clinical evidence of IgA nephropathy diagnosed by renal biopsy associated with COVID-19 vaccines published by 10 July 2022 with the largest sample size, and elaborate the hypothesis of pathogenesis between them.

Materials and methods

In this review, we searched relevant literatures published before 10 July 2022 through electronic databases, including PubMed, EMBASE and Web of Science, using the following keywords: ('immunoglobulin A nephropathy' OR 'IgA nephropathy' OR 'glomerulonephritis' OR 'nephropathies' OR 'hematuria') AND ('COVID-19' OR '2019-nCoV' OR 'SARS-CoV-2' OR 'novel corona virus' OR 'coronavirus') AND ('vaccine' OR 'vaccination'). Then, we extracted baseline characteristics, experimental data about presentations, treatments and responses.

We report medians and ranges for continuous data and numbers and percentages for categorical data. We used descriptive statistics in this report and perform statistical analysis. The Kolmogorov–Smirnov test was used to evaluate the distribution of the variable. Mann–Whitney test was used for continuous data and Chi-Square test was used for categorical data to determine whether the two groups were statistically different. Because our sample size is small and there are data with a theoretical frequency T-value <5, the continuity correction is used for the simple four-table data, and the Fisher's Exact test is used for the $R \times C$ table data. All statistical analyses were carried out by SPSS24.0 software and P-values <0.05 were considered to be statistically significant.

Results

Baseline demographic and clinical characteristics of IgA nephropathy patients

There are 32 IgA nephropathy articles related to COVID-19 vaccines from inception to 10 July 2022. A total of 48 patients were diagnosed with IgA nephropathy by renal biopsy, including 31 newly diagnosed IgA nephropathy (64.6%)[14–36] and 17 relapsed IgA nephropathy (35.4%).[18,22,30,37–45] The median age was 35 (12–79) years, and 47.9% (23 of 48 cases) of patients were male. Most patients were Asians (41.7%), followed by Americans (37.5%). In addition, 62.5% of our patients received BNT162b2 (Pfizer) vaccine, 31.3% received mRNA-1273 (Moderna) vaccine and another 6.3% received AstraZeneca vaccine (Table 1).

Most patients developed symptoms after the second dose (79.2%), with a median onset time of 2 (immediate—79) days. In contrast, 10 patients (20.8%) developed clinical symptoms after the first dose (9 patients had new diagnosis and 1 patient was recurrence), with a median onset time of 10 (1–61) days. Common clinical manifestations were gross hematuria (GH), acute kidney injury (AKI), proteinuria and fever. The median serum creatinine was 1.26 (0.47–3.57) mg/dl. In most patients, GH is usually self-limited and rarely requires immunosuppressive therapy. Of 48 patients, 19 received immunosuppressive therapy, of which 13 had clinically manifested AKI and the other 29 received conservative treatment. Follow-up data were available for 42 patients, 39 patients responded well to the treatments (14 with immunotherapy and 25 with conservative treatment), and only 3 patients from the newly diagnosed group showed no respond. The median time to remission of GH in patients receiving conservative treatment was 5.5 (2–30) days. The detailed baseline clinical characteristics of each patient are shown in Table 2.

Clinical characteristics and treatment of IgAN patients with new symptoms after the first dose of COVID-19 vaccination

There were 10 patients with clinical symptoms after the first dose of vaccine, of which 9 were new cases and 1 was a relapse, with a median onset time of 10 (1–61) days. Patients with Cases 3, 4 and 5 had a history of asymptomatic hematuria. Case 6 patient had history of inflammatory bowel disease and renal cell carcinoma. He underwent partial nephrectomy 7 years before vaccination, and in order to assess the presence of IgA deposits prior to vaccination, nephrectomy samples were retrieved for further examination. There were unremarkable in the glomeruli under the light microscope. Immunofluorescence detection of pronase-digested paraffin tissue revealed segmental mesangial staining for IgA, kappa and lambda. Electron microscopy showed the presence of mesangial deposits.

Of the 10 patients, 7 received immunotherapy and 3 received conservative treatment. Among the 7 patients receiving immunotherapy, 5 patients presented with clinical AKI, and 2 patients (Cases 1 and 8) received hemodialysis. The Case 7 patient had pericarditis symptoms in addition to GH and was treated with prednisone. Case 4 underwent two plasma exchanges to rule out thrombotic thrombocytopenic purpura because of thrombocytopenia and pyuria after vaccination, and antibiotics therapy for possible pyelonephritis.

Of the 10 patients, 9 had received follow-up data from 1 week to 5 months, of which 6 patients responded well to the treatment. Case 8 died of sudden acute heart attack during the 2-month follow-up. Case 6 developed AKI and nephrotic-rang proteinuria after the first dose of Moderna vaccine and went on to receive the second dose of the vaccine. Kidney biopsy was diagnosed as IgA nephropathy with acute interstitial nephritis, and he treated with steroid pulse therapy, but the disease has progressed without responding. Relapsed Case 1 patient[37] was a 41-year-old woman with a previous diagnosis of IgAN who underwent kidney transplantation in 2013. The patient developed GH, proteinuria, slightly elevated creatinine and marked leukocytosis 2 days after receiving the first dose of mRNA vaccine, and the symptoms subsided spontaneously within a few days of observation.

Clinical characteristics and treatment of IgAN patients with new symptoms after the second dose of COVID-19 vaccination

There were 38 patients with clinical symptoms after the second dose of vaccine, of which 22 were new cases and 16 were

Table 1. Clinical characteristics of patients with IgAN post-COVID-19 vaccination

Characteristics	First dose ($n = 10$)	Second dose ($n = 38$)	Total ($n = 48$)	*P*
Age (year)	40.5 (12–79)	30 (13–73)	35 (12–79)	0.324
Male sex, *n* (%)	5 (50.0)	18 (47.4)	23 (47.9)	1.000
Geographic region, *n* (%)				0.216
Asia	4 (40.0)	16 (42.1)	20 (41.7)	
Europe	4 (40.0)	6 (15.8)	10 (20.8)	
USA	2 (20.0)	16 (42.1)	18 (37.5)	
Medical history, *n* (%)				
Hypertension	0 (0)	5 (13.2)	5 (10.4)	
Autoimmune disease	2 (20.0)	20 (52.6)	22 (45.8)	
Kidney transplant	1 (10.0)	2 (5.3)	3 (6.3)	
Abnormal urine	3 (30.0)	11 (28.9)	14 (29.2)	
Vaccine type, *n* (%)				0.127
BNT162b2 (Pfizer)	6 (60.0)	24 (63.2)	30 (62.5)	
mRNA-1273 (Moderna)	2 (20.0)	13 (34.2)	15 (31.3)	
Adenovirus vector (AstraZeneca)	2 (20.0)	1 (2.6)	3 (6.3)	
Cases, *n* (%)				0.129
New cases	9 (90.0)	22 (57.9)	31 (64.6)	
Relapsed cases	1 (10.0)	16 (42.1)	17 (35.4)	
Timing of symptom onset, *n* (%)				0.030[a]
1 day	2 (20.0)	18 (47.4)	20 (41.7)	
2–7 days	2 (20.0)	14 (36.8)	16 (33.3)	
>7 days	6 (60.0)	6 (15.8)	12 (25.0)	
Timing of symptom onset, days				
New cases	11 (1–61)	2 (1–42)	2 (1–61)	0.045
Relapsed cases	2	1.5 (1–79)	2 (1–79)	0.745
Symptoms, *n* (%)				
GH	7 (70.0)	33 (86.8)	40 (83.3)	
AKI	5 (50.0)	14 (36.8)	19 (39.6)	
Proteinuria	10 (100)	32 (84.2)	42 (87.5)	
Fever	3 (30.0)	17 (44.7)	20 (41.7)	
Laboratory on presentation				
Serum creatinine (mg/dl)	1.5 (0.58–3.57)	1.23 (0.47–3.53)	1.26 (0.47–3.57)	0.670
Treatment, *n* (%)				0.065
Conservative management	3 (30.0)	26 (68.4)	29 (60.4)	
Steroid	7 (70.0)	12 (31.6)	19 (39.6)	
Outcome, *n* (%)				0.479
Response	7 (70.0)	32 (84.2)	39 (81.3)	
Not response	1 (10.0)	2 (5.3)	3 (6.3)	

Patients with a history of autoimmune disease or abnormal urinalysis may have asymptomatic IgAN.
[a]Statistically different.

recurrent cases, with a median onset time of 2 (immediate—79) days. Case 17 patient in the recurrence group relapsed after receiving the second dose of the vaccine and was found to have worsening proteinuria on Day 79, resulting in a delayed diagnosis of IgA nephropathy. Pathology showed the presence of mixed cells and fibrocytic crescents, indicating that disease reactivation occurred several weeks before the biopsy time, which may be closer to the time of vaccination. Of the 22 newly diagnosed patients, 9 had a previous history of hematuria and 4 had autoimmune diseases. Autoimmune disorders include a history of inflammatory bowel disease, antiphospholipid syndrome and glomerulonephritis. Case 17 had a history of chronic kidney disease and mild proteinuria. Case 13 had a history of foamy urine and a renal biopsy with cellular glomerular crescents and moderate to severe renal tubulointerstitial scarring. Case 15 had a history of gestational diabetes mellitus, and histopathology suggested chronic disease. Renal biopsy in Cases 21 and 22 showed focal glomerular and tubulointerstitial scarring.

Of the 38 patients, 12 received immunotherapy and 26 received conservative treatment. Among the 12 patients receiving immunotherapy, 8 patients presented with clinical AKI. Case 23 had persistent proteinuria and microhematuria and underwent tonsillectomy and steroid pulse therapy.

Of the 38 patients, 34 had access follow-up data from 2 days to 5 months, of which 32 patients responded well to the treatment. Case 30 patient,[33] a 73-year-old man with previous aristolochic acid nephropathy (AAN) and hypertension, underwent bilateral nephrectomy and kidney transplantation. The patient developed edema of the lower legs, proteinuria and hematuria 5 weeks after the second adenoviral vector vaccine, and was treated with angiotensin-converting enzyme inhibitor to optimize antihypertensive therapy, and the disease progressed 3 weeks later. Case 31 patient[34] was a 30-year-old man with a previous diagnosis of membranous proliferative glomerulonephritis type 1 who received a kidney transplant in 2019. Thirty-four days after receiving the second dose of mRNA

Table 2. Summary of published cases of IgAN following COVID-19 vaccination

No.	Authors	Age/sex	Country (race)	Medical history	Baseline (hhematuria/proteinuria/SCr)	Vaccine	Timing of symptom onset	Symptoms	Urinalysis	Blood test	Renal biopsy (MEST-C)	Treatments	Outcomes
New cases													
1	Niel[14]	13/F	Luxembourg	None	NA	mRNA (Pfizer)	< D1 after 1st dose	GH, AKI, NRP, fever, asthenia, muscle pain	proteinuria: 3.9 g/l	SCr: 3.57 mg/dl	IgAN (M1E1S0T0)	Hemodialysis + high-dose steroid	R. SCr improved to normal level within D30, microhematuria and a slight proteinuria persisted.
2	Abdel-Qader[15]	12/M	Jordanian	None	Normal	mRNA (Pfizer)	< D1 after 1st dose	GH, AKI, NRP, HTN, fever, fatigue	RBC: 1920/μl, proteinuria: 1.7 g/l	SCr: 1.77 mg/dl (D2)	IgAN	High-dose steroid	R. Remission of GH, AKI, proteinuria within D7
3	Okada[16]	17/F	Japan	Asymptomatic hematuria	Microscopic hematuria	mRNA (Pfizer)	D4 after 1st dose	GH, SRP	UPCR: 0.37 g/g	SCr: 0.58 mg/dl, IgG: 10.171 g/L, C3: 0.907 g/l	IgAN (M0E0S0T0)	Conservative	CR. Hematuria changed to microscopic within 1 week, and proteinuria resolved spontaneously with D10 after 2nd dose
4	Fujita[17]	40/F	Japan	Occult blood	SCr: 0.76 mg/dl	mRNA (Pfizer)	D9 after 1st dose	GH, NRP, fever, chills, shivering, thrombocytopenia, pyuria	RBC: 100/HPF, UPCR: 18.13 g/g, WBC: 5–9/HPF	SCr: 0.86 mg/dl (D9), 1.23 mg/dl (D15), albumin: >3 g/dl, IgA: 155 mg/dl, C3: 88 mg/dl	IgAN (M1E0S0T0C1)	Conservative, plasma exchange, ABPC/SBT	CR. Proteinuria spontaneously resolved within D15, GH changed to microscopic within D15, SCr improved to within normal level within later 2 months.
5	Yokote[35]	36/F	Japan	Microscopic hematuria, proteinuria, rheumatoid arthritis	NA	mRNA (Pfizer)	D11 after 1st dose	GH, NS	UPCR: 15.6 g/g, RBC: >100/HPF	SCr: 0.9 mg/dl, ALB: 1.9 g/dl	DPGN, IgAN (M1E1S1T0C0)	High-dose steroid + immunosuppressive	R. UPCR improved to 2.9 g/g within 4 weeks. RBC and ALB were 30-49/HPF and 3.2 g/dl within 8 weeks, respectively.
6	Klomjit[18]	44/M	USA (White)	NA	SCr: 1.1 mg/dl	mRNA (Moderna)	D14 after 1st dose	AKI, NRP	RBC: 21–30/HPF, UTP: 14 g/d	SCr: 2.5 mg/dl	IgAN, AIN	High-dose steroid	NR. SCr, RBC and UTP were 3.6 mg/dl, 3-10/HPF and 5.6 g/d within 3 months, respectively.
7	Klomjit[18]	66/M	USA (White)	NA	SCr: 1.1 mg/dl	mRNA (Moderna)	D14 after 1st dose	GH, SNP, pericarditis	RBC: 51–100/HPF, UTP: 1.2 g/d	SCr: 1.5 mg/dl, 2.2 mg/dl (2nd dose)	IgAN	Prednisone[a]	R. Scr, RBC and UTP were 1.4 mg/dl, 3–10/HPF and 0.3 g/d within 5 months, respectively.
8	Fenoglio[19]	74/M	Italy	NA	Normal	Adenovirus vector (AstraZeneca)	D42 after 1st dose	RF, NS	NA	NA	IgAN	Steroid + hemodialysis	NA Died after 2 months of follow-up to acute heart attack.
9	Fenoglio[19]	79/M	Italy	NA	Normal	Adenovirus vector (AstraZeneca)	D61 after 1st dose	RF, NS	NA	NA	IgAN	Steroid + immunosuppressive	NA
10	Anderegg[20]	39/M	Switzerland	HTN	NA	mRNA (Moderna)	Immediate after 2nd dose	GH, AKI, SRP, flu-like symptoms, severe fever	Numerous RBC	AKI	IgAN	High-dose steroid + immunosuppressive	R. SCr was normalized and proteinuria significantly decreased, but microhematuria persisted within several weeks

(continued)

Table 2. (continued)

No.	Authors	Age/sex	Country (race)	Medical history	Baseline (hhematuria/proteinuria/SCr)	Vaccine	Timing of symptom onset	Symptoms	Urinalysis	Blood test	Renal biopsy (MEST-C)	Treatments	Outcomes
11	Lo[21]	28/F	China	Microscopic hematuria	SCr: 0.66 mg/dl, UPCR: 20 mg/mmol	mRNA (Pfizer)	3 h after 2nd dose	GH, SRP	UPCR: 320 mg/mmol	SCr: 0.81 mg/dl, ANA: 1:640	IgAN (M1E0S0T0C0)	Conservative	CR. SCr improved to within normal level and hematuria subsided spontaneously in D5, UPCR fell to 34 mg/mmol and ANA became negative within 3 weeks
12	Yotoke[35]	19/M	Japan	Microscopic hematuria	NA	mRNA (Pfizer)	18h after 2nd dose	GH	RBC: 50–99/HPF, UPCR: 1.5 g/g	SCr: 0.97 mg/dl	DPGN, IgAN (M1E1S1T0C1)	RASi	R. UPCR improved to <1 g/g within 12 weeks.
13	Hanna[22]	17/M	USA (White)	Foamy urine	NA	mRNA (Pfizer)	< D1 after 2nd dose	GH, AKI, SRP, HTN grade 1	UPCR: 1.75 g/g (D9)	SCr: 1.78 mg/dl (D6), ALB: 3.8 g/dl	IgAN (M1E1S1T1C1)	High-dose steroid	R. Hematuria self-resolved in D4 and SCr improved to 1.2 mg/dl at D22
14	Abramson[23]	30/M	USA (European and American ancestry)	None	NA	mRNA (Moderna)	D1 after 2nd dose	SRP, fevers, chills, headache, brown-colored urine	UPCR: 0.8 g/g, RBC: >30/HPF, WBC: 11–30/HPF	SCr: 1.02 mg/dl, IgA: 444 mg/dl	IgAN (M1E0S1T0C0)	RASi	R. GH changed to microscopic within D2, UPCR improved to 0.43 g/g within 6 weeks
15	Tan[24]	41/F	Chinese	GDM	Normal	mRNA (Pfizer)	D1 after 2nd dose	AKI, GH, SRP, HTN grade 1, headache, generalized myalgia	RBC: >200 μl, UPCR: 2.03 g/g	SCr: 1.73 mg/dl, IgG : 12.9 g/l, C3:0.83 g/l, ANA : 1:320	IgAN	High-dose steroid + immunosuppressive	NA.
16	Leong[25]	26/M	Singapore	Suspected IgAN	SCr: 0.85 mg/dl, UPCR: 74 mg/mmol	mRNA (Pfizer)	D1 after 2nd dose	GH, AKI, SRP, fever	UPCR: 174 mg/mmol, RBC: >100/HPF	SCr: 1.62 mg/dl, ALB: 4 g/dl	IgAN	RASi	NA
17	Park[26]	50/M	USA	HTN, CKD, mild proteinuria	SCr: 1.17 mg/dl, RBC: 11–25/HPF, UPCR: 2.4 g/g	mRNA (Moderna)	D1 after 2nd dose	GH, AKI, NRP	RBC: >50/HPF, UPRC: 3.56 g/g,	SCr: 1.54 mg/dl	IgAN	RASi	R. RBC, UPCR and SCr were 11–25/HPF, 2.2 g/g, 1.24 mg/dl following up 1 month, respectively.
18	Lim[27]	42/F	Korea	None	NA	mRNA (Moderna)	D1 after 2nd dose	GH	UTP :1.7 g/d	SCr: 0.47 mg/dl	IgAN (M0E1C1S1T0)	RASi	PR. GH disappeared within several days, but microhematuria and proteinuria persisted.
19	Uchiyama[36]	15/M	Japan	Microscopic hematuria	NA	mRNA (Pfizer)	D1 after 2nd dose	GH, fever, myalgia	UPCR: 0.9 g/g, numerous RBC	SCr: 0.97 mg/dl	IgAN (M1E0S0T0C1)	Conservative	R. GH spontaneously resolved within D6. Microhematuria and proteinuria persisted.
20	Uchiyama[36]	18/M	Japan	Microscopic hematuria	NA	mRNA (Pfizer)	D2 after 2nd dose	GH, fever, general malaise	UPCR: 0.4 g/g numerous RBC	SCr: 0.82 mg/dl	IgAN (M1E0S0T0C0)	Conservative	R. GH spontaneously resolved within D7. Microhematuria and proteinuria disappeared gradually.

(continued)

Table 2. (continued)

No.	Authors	Age/sex	Country (race)	Medical history	Baseline (hhematuria/proteinuria/SCr)	Vaccine	Timing of symptom onset	Symptoms	Urinalysis	Blood test	Renal biopsy (MEST-C)	Treatments	Outcomes
21	Kudose[28]	50/F	USA (White)	HTN, APS, obesity	SCr: 1.3 mg/dl, RBC: 10–20/HPF, UPCR: 1.3 g/g	mRNA (Moderna)	D2 after 2nd dose	GH, AKI, SRP, fever, body aches	UPCR: 2 g/g, RBC: >50/HPF	SCr: 1.7 mg/dl	IgAN (M1E0S1T1C1)	Conservative	R. Hematuria resolved within D5.
22	Kudose[28]	19/M	USA (White)	Microscopic hematuria	Normal	mRNA (Moderna)	D2 after 2nd dose	GH	numerous RBC	SCr: 1.2 mg/dl	IgAN (M1E1S1T0C0)	Conservative	R. Hematuria resolved within D2.
23	Horino[29]	17/M	Japan	Microscopic hematuria	NA	mRNA (Pfizer)	D2 after 2nd dose	GH, SRP, fever, headache,	UPCR: 1.0 g/g, RBC: >100/HPF	SCr: 0.70 mg/dl, CRP: 2.41 mg/dl	IgAN	Tonsillectomy + high-dose steroid	PR. Proteinuria and microhematuria persisted within 2 months later
24	Srinivasan[30]	35/M	USA (Caucasian)	Nephrolithiasis, ulcerative colitis	SCr: 1 mg/dl	mRNA (Moderna)	D2 after 2nd dose	GH, AKI, SRP	UPCR: 0.656 g/g	SCr: 1.3 mg/dl	IgAN (M1E1S0T0C1)	Immunosuppressive	PR. Hematuria resolved, SCr and UPCR returned to stable but not back to baseline within 4 weeks
25	Morisawa[31]	16/M	Japan	Asymptomatic hematuria	SCr: 0.87 mg/dl, RBC: 50–100/HPF, UPCR: 0.03 g/g	mRNA (Pfizer)	D2 after 2nd dose	GH, AKI, SRP, fever	UPCR: 0.28 g/g (D6), 0.35 g/g (D21)	SCr: 1.1 mg/dl (D6), 1.26 mg/dl (D20), 1.29 mg/dl (D55)	IgAN (M0E1S0T0C1)	Steroid + immunosuppressive	R Remission of GH after D3, AKI after 3 months
26	Morisawa[31]	13/F	Japan	Asymptomatic hematuria	SCr: 0.51 mg/dl, RBC: 10–20/HPF, UPCR: 0.08 g/g	mRNA (Pfizer)	D2 after 2nd dose	GH, SRP, fever	UPCR: 1.99 g/g (D7)	SCr: 0.54 mg/dl	IgAN (M0E0S0T0C0)	Conservation	R Resolved of UPCR in 26 days.
27	Nihei[32]	28/F	Japan	GH and mild proteinuria in 17 years old	NA	mRNA (Pfizer)	D7 after 2nd dose	GH	RBC: >100/HPF, UPCR: 0.13 g/g, Gd-IgA1: 23 ng/ml	C3: 85 U/L, IgA: 283 mg/dl, SCr: 0.7 mg/dl, Gd-IgA1: 4 μg/ml	IgAN (M0S0E1T0C0)	Conservative	CR Proteinuria and hematuria resolved in 28 days.
28	Klomjit[18]	38/M	USA (White)	NA	SCr: 1.3 mg/dl	mRNA (Pfizer)	D14 after 2nd dose	GH, SRP	RBC : 51–100/HPF UTP: 0.32 g/d	SCr: 1.6 mg/dl	IgAN	Conservative	NA
29	Alonso[34]	30/M	Spain	Membranous proliferative glomerulonephritis type 1, CKD, KT (2019)	SCr: 1.1 mg/dl, UACR: 0.45 g/g	mRNA (Pfizer)	D34 after 2nd dose	Microscopic hematuria	UACR: 0.4 g/g, hematuria: 150/μl	SCr: 1.65 mg/dl, 2.4 mg/dl (D50)	IgAN	Steroid	NR. Hematuria, UACR and SCr were 30/μl, 0.47 g/g and 1.9 mg/dl within after 2 months, respectively.
30	Mokos[33]	73/M	Croatia	AAN, HTN, KT	UTP: 0.25 g/d	Adenovirus vector (AstraZeneca)	D35 after 2nd dose	SRP, edema of the lower legs	UTP: 1.4 g/d, RBC: 3–5/HPF	SCr: 1.67 mg/dl	IgAN (M0E1S0T0C1)	RASi	Progressed. UTP and RBC were 1.9 g/d, 5–10/HP during the next 3 weeks, respectively.
31	Klomjit[18]	62/M	USA (White)	NA	SCr: 1.0 mg/dl	mRNA (Pfizer)	D42 after 2nd dose	AKI, SRP	RBC: 31–40/HPF, UTP: 0.9 g/d	SCr: 2.2 mg/dl	IgAN	Conservative	R. SCr, RBC and UTP were 2.0 mg/dl, <3/HPF and 0.2 g/d within 1.5 months, respectively
Relapsed cases													
1	Perrin[37]	41/F	France	IgAN (2005), KT (2013)	Microscopic hematuria	mRNA (Pfizer)	D2 after 1st dose	GH, SRP, marked leukocytosis	UPCR: 0.47 g/g, numerous RBC	SCr transiently increased	IgAN	Conservative	CR. Symptoms spontaneously resolved.

(continued)

Table 2. (continued)

No.	Authors	Age/sex	Country (race)	Medical history	Baseline (hhematuria/proteinuria/SCr)	Vaccine	Timing of symptom onset	Symptoms	Urinalysis	Blood test	Renal biopsy (MEST-C)	Treatments	Outcomes
2	Horino[38]	46/F	Japan	IgAN, tonsillectomy	SCr was normal, RBC: <5/HPF	mRNA (Pfizer)	12h after 2nd dose	GH, SRP, fever, myalgia	proteinuria: 3+, RBC: >100/HPF	SCr was normal	IgAN	Conservative	PR. Proteinuria spontaneously resolved within 2 weeks, GH changed to microscopic within 2 weeks.
3	Negrea[39]	38/F	USA (White)	IgAN (2005)	UTP: 0.63 g/d, Microscopic hematuria	mRNA (Moderna)	8–24 h after 2nd dose	GH, SRP, fever, body aches, chills, headache, fatigue	UTP: 0.82 g/d	SCr was normal	IgAN	Conservative	PR. Hematuria spontaneously resolved in 3 d, proteinuria was 1.4 g/d within 3 weeks.
4	Negrea[39]	38/F	USA (White)	IgAN (2019)	UTP: 0.43 g/d, Microscopic hematuria	mRNA (Moderna)	8–24 h after 2nd dose	GH, SRP, fever, body aches, chills, headache, fatigue	UTP: 0.59 g/d	SCr was normal	IgAN	Conservative	CR. Hematuria spontaneously resolved in 3 d, proteinuria was 0.4 g/d within 3 weeks.
5	Valenzuela[45]	36/F	Spain	IgAN (2020)	SCr: 0.9 mg/dl, UTP: 0.7 g/d, Microhematuria	mRNA (Moderna)	Few hours after 2nd dose	GH, AKI, fever, malaise	UTP: 1.5 g/d	SCr: 1.8 mg/dl, IgA: 2174 mg/l	IgAN	High-dose steroid + immunosuppressive	R. SCr and proteinuria were 1.09 mg/dl and 0.5 g/d after 2 months, respectively.
6	Rahim[40]	52/F	Asian	IgAN (2017)	ACR: <1 g/g	mRAN (Pfizer)	< D1 after 2nd dose	GH, SRP, fever, generalized myalgias, lumbago bilaterally	numerous RBC, ACR: 2.4 g/g	NA	IgAN	Conservative	CR. Hematuria resolved within 1 week, ACR was 1.44 g/g within D5.
7	Plasse[41]	NA	USA	IgAN (2020)	SCr: 1.0 mg/dl, UPCR: 0.61 mg/g	mRNA (Pfizer)	< D1 after 2nd dose	GH, body aches	UPCR: 0.92 mg/g, numerous RBC	SCr: 1.16 mg/dl	IgAN	Conservative	CR. Hematuria resolved within D3.
8	Hanna[22]	13/M	USA (White)	IgAN, T1DM	SCr: 0.54 mg/dl, UPCR: 1.6 g/g, ALB: 3.4 g/dl	mRNA (Pfizer)	< D1 after 2nd dose	GH, SRP, AKI, vomiting	UPCR: 1.07 g/g, numerous RBC	SCr: 1.31 mg/dl (D2), ALB: 3.8 g/dl	IgAN (M0E0S0T0C0)	Conservative	CR. Hematuria and AKI resolved within D6, UPCR was 0.86 g/g (D6).
9	Srinivasan[30]	25/F	European	IgAN	SCr: 0.7 mg/dl, UPCR: 1.41 g/g	mRNA (Moderna)	D1 after 2nd dose	GH, AKI, NRP	UPCR: 4.76 g/g	SCr: 1.07 mg/dl	IgAN	Conservative	CR. Hematuria resolved, SCr and UPCR returned to baseline within 3 weeks.
10	Perrin[37]	27/F	France	IgAN (2020), HD	Normal	mRNA (Pfizer)	D2 after 2nd dose	GH, SRP, abdominal pain, urticaria at D5, moderate pancytopenia,	UPCR: 1.9 g/g, numerous RBC	NA	IgAN	Conservative	R. Symptoms spontaneously resolved, UPCR was 1.2 g/g within 1 month after 2nd dose.
11	Watanabe[42]	54/F	USA (Caucasian)	IgAN (2006), obesity, HTN, GERD	SCr: 1.2 mg/dl, UPCR: 1.03 g/g, RBC: 15/HPF	mRNA (Moderna)	D2 after 2nd dose	GH, AKI, SRP	RBC: 50/HPF, UPCR: 0.67 g/g	SCr: 3.04 mg/dl (D7)	Active IgAN	Steroids	R. Remission of GH after 2 days, AKI in 3 months.
12	Udagawa[43]	15/F	Japan	IgAN	NA	mRNA (Pfizer)	D2 after 2nd dose	GH, SRP, fever	numerous RBC, mild proteinuria	SCr was normal	IgAN	Conservation	R. Remission of GH after 3 days.
13	Udagawa[43]	16/F	Japan	IgAN	Normal	mRNA (Pfizer)	D3 after 2nd dose	GH, fever, headache	numerous RBC	SCr was normal	IgAN	Conservation	R. Remission of GH after 2 days.

(continued)

Table 2. (continued)

No.	Authors	Age/sex	Country (race)	Medical history	Baseline (hhematuria/proteinuria/SCr)	Vaccine	Timing of symptom onset	Symptoms	Urinalysis	Blood test	Renal biopsy (MEST-C)	Treatments	Outcomes
14	Plasse[41]	NA	USA	IgAN (2018)	SCr: 0.8 mg/dl, UPCR: 1.56 mg/g	mRNA (Pfizer)	D5 after 2nd dose	GH, AKI, fevers, chills, body aches, dysuria	UPCR: 3.0 mg/g, numerous RBC	SCr: 3.53 mg/dl	IgAN	Steroids	R. SCr and proteinuria recovered baseline within 1 month and 2 months, respectively.
15	Klomjit[18]	19/M	USA (White)	IgAN	SCr: 0.96 mg/dl	mRNA (Moderna)	D7 after 2nd dose	GH, SRP	RBC: 50–100/HPF, UTP: 0.61 g/d	SCr: 0.76 mg/dl	IgAN	Conservative	NA.
16	Yokote[35]	48/F	Japan	IgAN (M0E1S1T0-C1), tonsillectomy	UTP: 0.91 g/d	mRNA (Pfizer)	D14 after 2nd dose	NS, GH	RBC: >100/HPF, UPCR: 19.05 g/g	SCr: 0.94 mg/dl ALB: 2.2 g/dl	DPGN, IgAN (M0E1S1T0C1)	High-dose steroid	PR. UPCR was 6 g/g within 4 weeks.
17	Schaubschlager[44]	35/F	USA	IgAN, psoriasis	SCr: 1.0 mg/dl, UPCR: 0.36 g/g	mRNA (Pfizer)	D79 after 2nd dose	SRP	UPCR: 2 g/g	SCr: 1.1 mg/dl	IgAN (M1E1S1T0C1)	High-dose steroid + immunosuppressive	R. UPCR was 1.14 g/g within 4 weeks.

[a]Prednisone was initiated for the treatment of pericarditis.

COVID-19, coronavirus disease 2019; IgAN, IgA nephropathy; F, female; M, male; GH, gross hematuria; SRP, sub-nephrotic range proteinuria; NRP, nephrotic range proteinuria; SCr, serum creatinine; ANA, anti-nuclear antibody; C3, complement C3; CRP, C-reactive protein; ALB, serum albumin; RBC, red blood cell; WBC, white blood cell; HPF, high power field; UPCR, urine protein-to-creatinine ratio; UACR, urinary albumin-creatinine ratio; ACR, microalbumin-creatinine ratio; UTP, 24-h urine protein; CR, complete remission; PR, partial remission; NA, non-applicable; NR, no response; R, response; KT, kidney transplantation; HD, hemodialysis; RASi, renin–angiotensin–aldosterone system inhibition; ABPC, ampicillin; SBT, sulbactam; HTN, hypertension; T1DM, type 1 diabetes mellitus; AIN, acute interstitial nephritis; DPGN, diffuse proliferative glomerulonephritis; APS, antiphospholipid syndrome; GDM, gestational diabetes; AAN, aristolochic acid nephropathy; RF, renal failure; NS, nephrotic syndrome; AKI, acute tubular injury; GERD, gastroesophageal reflux disease; CKD, chronic kidney disease; MEST-C, M = mesangial hypercellularity, E = endocapillary proliferation, S = segmental glomerulosclerosis, T = tubular atrophy/interstitial fibrosis, C = crescents.

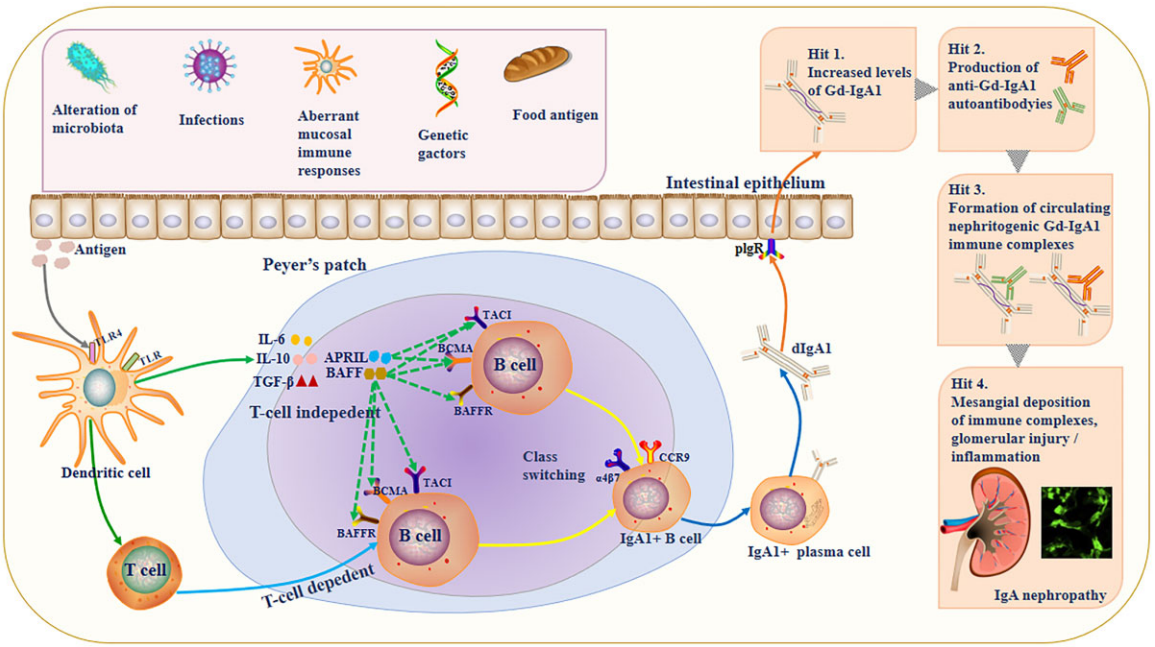

Figure 1. Mucosal immune anatomy of IgA responses and the 'multi-hit' model of IgAN. IgA is the most abundant antibody isotype in the body, with the majority of IgA found in mucosal secretions. Mucosal IgA production is induced by T-cell-dependent and T-cell-independent mechanisms. In individuals with a genetic predisposition to IgA nephropathy, chronic bacterial infection and gut dysbiosis initiate T-cell-independent pathways that trigger the expression of TLRs on antigen-presenting cells that recognize pathogens and release a variety of lymphocyte inflammatory cytokines, such as IL-6, IL-10, IL-21, BAFF, TGF-β and APRIL, stimulate B-cell differentiation and proliferation, have class switching from IgM to IgA1. IgA-secreting plasma cells migrate to lamina propria, where they release dimeric IgA1 (dIgA1). The dimers are formed through an interaction of two IgA1 molecules with a joining chain (J-chain), which is synthesized by plasma cells. IgA1 dimers can bind to the polymeric Ig receptor (pIgR) on the basolateral surface of the mucosal epithelium and undergo transcytosis to the apical surface, where they dissociate from pIgR and are secreted into the lumen carrying the secretory component of the receptor. In the T-cell-dependent pathway, B-cell type switching occurs after antigen-specific T-cell activation. The level of IgA1 bearing galactose-deficient O-glycans (Gd-IgA1) is increased in the circulation of patients with IgA nephropathy (hit 1). These IgA1 glycoforms are recognized as autoantigens by antiglycan autoantibodies (anti-Gd-IgA1 autoantibodies; hit 2), resulting in the formation of nephritogenic immune complexes (hit 3), some of which deposit in the kidney and activate mesangial cells (hit 4). Mesangial cells start to proliferate and overproduce components of extracellular matrix, cytokines and chemokines. Some of these cytokines can then cause podocyte injury and induce proteinuria. The figure refers to the pathogenesis of IgAN by Gesualdo *et al.*[51]

vaccine, the patient developed microhematuria and proteinuria, and his creatinine progressed to 2.4 mg/dl. He received oral prednisone, and his condition did not improve after 1 month.

Discussion

'Multi-hit' hypothesis of IgA nephropathy

IgA nephropathy, the most common primary glomerulonephritis worldwide, is characterized by mesangial immunodeposits of IgA1 with mesangial proliferation.[46] Several studies have shown that IgA nephropathy is an autoimmune disease with multiple pathogenic mechanisms involving genetically susceptible variants encoding galactosylation, aberrant mucosal immune responses and environmental triggers such as infection, alteration of microbiota and food antigen.[47] At present, the pathogenesis of IgAN is still unclear, and the most widely accepted mechanism is the 'multi-hit' theory.[13,48] Specifically, hit 1 is an increase in circulating IgA1 deficient in O-glycosylation of the hinge region. Hit 2 is the formation of antiglycan-specific IgG and/or IgA1 autoantibodies. Hit 3 is the formation of circulating immune complexes of galactose-deficient IgA1 (Gd-IgA1) and antiglycan IgG autoantibodies. Hit 4 is the deposition of circulating immune complexes in the mesangial area of the glomerulus, and complement activation causes multicellular damage to mesangial cells, podocytes and tubular epithelial cells (Figure 1).[49] IgA nephropathy patients usually present with asymptomatic microscopic hematuria or proteinuria. However, some patients have prodromal symptoms such as upper respiratory (tonsillitis or pharyngitis) and gastrointestinal infections with hours or days before the onset, and dimeric IgA1 is usually produced on the mucosal surface.[50] Therefore, aberrant mucosal immune response is considered to be involved in the pathogenesis of IgAN.[51]

Mucosal origin of hypogalactosylated IgA1 in IgAN

Chronic bacterial infection and gut dysbiosis initiate T-cell-independent pathways that trigger the expression of Toll-like receptors (TLR) on antigen-presenting cells (e.g. monocytes/macrophages, dendritic cells, neutrophils) that recognize pathogens and release a variety of lymphocyte inflammatory cytokines, such as interleukin (IL)-6, IL-10, IL-21, B-cell-activating factor (BAFF), transforming growth factor (TGF)-B and aproliferation inducing ligand (APRIL), especially BAFF and APRIL may bind to tumor necrosis factor (TNF) receptor homologous transmembrane activator,[52] stimulate B-cell differentiation and proliferation, have class switching from IgM to IgA1 and promote IgA overproduction.[53–55] In the T-cell-dependent pathway, B-cell type switching occurs after antigen-specific T-cell activation.[56] In the tonsil-renal axis, recent data show increased expression of TLR9 in tonsillar B cells of IgAN patients, which has specific activity to recognize bacterial and viral unmethylated deoxycytidyl-deoxyguanosine oligodeoxynucleotides (CpG-ODN). CpG-DON activates TLR9, increases the expression of APRIL,[57] BAFF[58] and IL-6, which induces the overproduction of

aberrantly glycosylated IgA via T-cell-independent pathway.[59] In the gut-renal axis, TLRs are highly expressed on mucosal epithelial cells, and they recognize molecular patterns of microorganisms and their products, such as lipopolysaccharide (LPS). Microbiota signaling through activation of TLRs may affect intestinal repair and damage, as well as increased intestinal permeability, which promotes the absorption and blood circulation of the bacterial product LPS. LPS is a ligand for TLR4. One study showed that LPS cultured by B lymphocytes activates TLR4, methylates the cosmc gene, reduces galactosyltransferase activity and leads to a decrease in the level of galactosylation modification of IgA1 molecules.[60,61] The innovative drug NEFECON is an oral targeted delayed-release preparation of budesonide. It can precisely deliver budesonide to the enrichment area of Peyer's patches in the terminal ileum for release and play a role in the source of intestinal mucosa immunity producing galactose-deficient IgA1, thereby inhibiting the occurrence and development of IgAN, reducing proteinuria and stabilizing renal function in patients.[62,63]

Hypothesis of IgAN caused by COVID-19 vaccination

Among reported patients with new cases, five patients showed chronic characteristic changes or moderate to severe tubulointerstitial scarring on renal biopsy,[17,22,24,28] suggesting that they had potential pre-existing IgAN, exacerbated by vaccination. Abnormal urinalysis performed before vaccination in 10 patients showed a history of hematuria,[16,21,29,31,32,36] 1 patient had a history of chronic kidney disease and mild proteinuria[26] and 1 patient was suspected of IgA nephropathy,[25] therefore, we suspect that IgA nephropathy is pre-existing and exacerbated by vaccination. One patient had a history of ulcerative colitis, and another patient had a history of rheumatoid arthritis in addition to hematuria and proteinuria, and this potential immune dysregulation raised the possibility that he might have had IgA deposits in his kidney and possibly asymptomatic IgAN before vaccination.[30] One patient had a history of inflammatory bowel disease and renal cell carcinoma.[18] He underwent partial nephrectomy 7 years before vaccination, and a review of the sample confirmed IgA deposition. These cases demonstrate that some of the new cases are 'relapses' of occult IgAN.

IgAN is the most common glomerular disease after COVID-19 vaccination, but the explanation for their association has not been fully established. One possible explanation for the development of IgAN in patients is the production of excess antiglycan antibodies following the COVID-19 vaccine, which cross-react with pre-existing Gd-IgA1.[23] Of the reported cases, 13 patients[21,22,24,26–28,30,37,41,42] developed GH, proteinuria and AKI within 2 days of the second dose. In patients with genetic predisposition, the disease may be in a latent state or in remission before COVID-19 vaccination, and there is a small amount of Gd-IgA1 or anti-glycan antibodies in the body, which does not cause clinical symptoms. Studies had shown that the COVID-19 mRNA vaccine in healthy adults was effective in inducing exponential increases in spike antigen-specific IgA and IgG serum levels, and further increases in IgA and IgG levels after the second vaccination,[64] while vaccination also stimulates spike-specific T-cell responses that were more readily detectable 7 days after secondary immunization.[65–67] The $CD4^+$ T-cell response is primarily directed against helper T-cell type 1, which produces interferon-c (IFN-c), TNF-α and IL-2. The main responses of $CD8^+$ T cells are IFN-γ and TNF.[65] After vaccination against COVID-19, the antibody titers in patients increases exponentially, leading to disease outbreaks. Therefore, we hypothesized that one possible explanation for the development of IgA nephropathy after COVID-19 vaccination is the production of excess antiglycan antibodies (Figure 2).

The second possible explanation, given elevated IgA levels, is an increase in pathogenic IgA production similar to the influenza vaccine. Of the reported cases, 17 patients developed new symptoms 3 days after vaccination. One patient had an episode of GH on Day 7 after the second dose of COVID-19 vaccine and a renal biopsy performed an additional 14 days showed the deposition of Gd-IgA1 and complement 3 in the mesangial region, and the author also found elevated urinary Gd-IgA1 levels.[32] Although the correlation between serum Gd-IgA1 levels and disease activity could not be detected. This case also suggests that an enhanced immune response to the mRNA vaccine may transiently increase Gd-IgA1 production, resulting in GH. The study had shown strong spike antigen-specific IgA and IgG responses in healthy individuals following mRNA vaccination. Serum levels of spike antigen-specific IgA were significantly lower than IgG levels, with spike-specific IgA decreasing to an average of 50% of peak levels between 1 and 2 vaccine injections, and decreased to 18% of peak levels during a follow-up period of more than 100 days after the second injection.[64] Although SARS-CoV-2 spike-specific serum IgA levels decline rapidly after infection, local concentrations on mucosal surfaces persist for longer, including dimeric subtype with strong neutralizing capacity, which was 15-fold higher than monomeric IgA.[68,69] Pathogenic IgA in IgAN patients is derived from dimeric IgA1. Therefore, we hypothesized that mRNA vaccination might result in increased serum Gd-IgA1 production. Parenteral influenza vaccines that do not activate mucosal immune responses are known to increase IgA levels.[70] Intramuscular inactivated influenza vaccine induced hyper-responsiveness of IgA1 monomers in a cohort of pre-existing IgAN patients.[71] Recurrence of IgAN following influenza vaccination has also been reported in kidney transplant recipients.[72]

The third possible explanation is that cytokine storm is involved in the development of disease. In addition to GH, AKI and proteinuria, 20 patients also showed systemic symptoms such as fever and pain. Two patients[14,15] developed symptoms within 24 h after the first dose of vaccine, 15 patients developed symptoms within 2 days after the second dose and 1 patient[20] had an attack immediately after administration. The rapidly developing clinical manifestations suggest systemic cytokine-mediated attack, possibly through the induction of enhanced IgA1 antiglycan immune response. These reports are similar to how infection with SARS-CoV-2 itself may be associated with the onset of potential autoimmune glomerular disease.[73] The receptor-binding domain of the SARS-CoV-2 spike protein is an immunodominant target for neutralizing antibodies in infected patients[74] and vaccinators.[75] It itself may act as a superantigen, causing the over-activation of the immune system, and the sharp rise of inflammatory factors such as IL-6, IL-10 and GM-CSF in the body, while GM-CSF will further activate $CD14^+$ and $CD16^+$ inflammatory monocytes cells, which produce a greater amount of IL-6 and other inflammatory factors, thus inducing systemic severe reaction and cytokine storm.[76,77] Among the reported cases of IgAN, three patients underwent kidney transplantation. Some studies have shown that the humoral and cellular immunity of kidney transplant patients after receiving the COVID-19 vaccine is significantly lower than that of healthy people.[78,79] Significant deterioration of IgAN may occur in the absence of anti-SARS-CoV-2 antibody response.

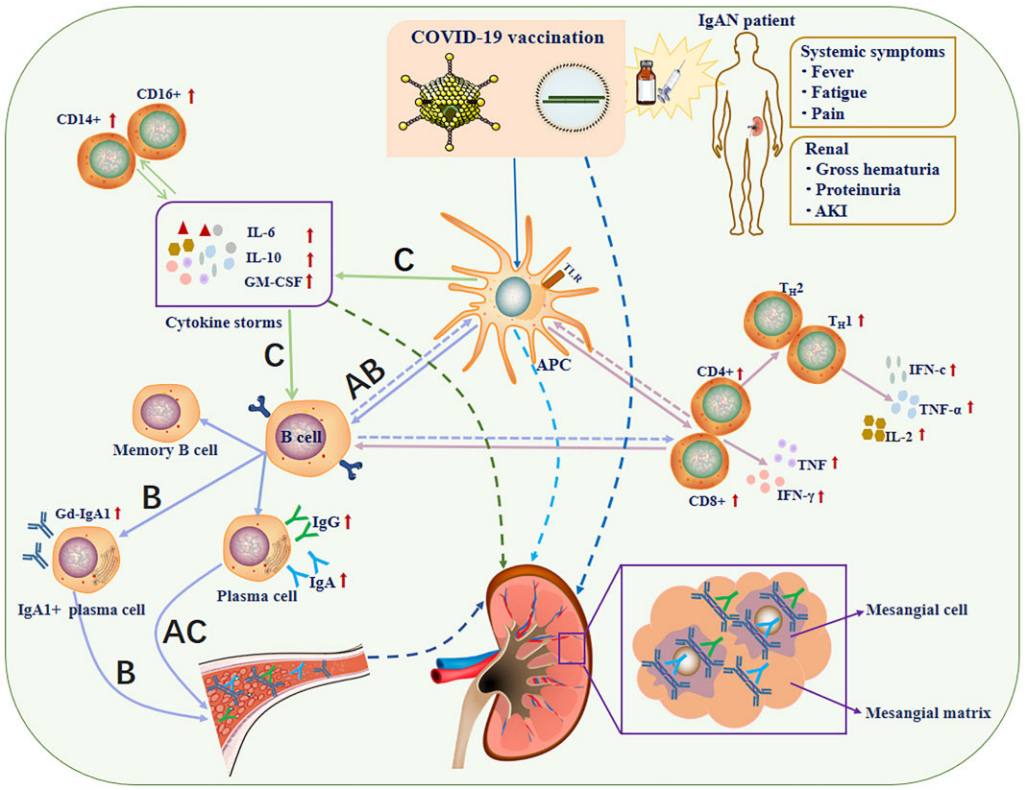

Figure 2. Hypothesis of IgAN caused by COVID-19 vaccination. The most common systemic symptoms in IgAN patients caused by COVID-19 vaccination were fever, fatigue and pain, and renal symptoms were GH, proteinuria and AKI. COVID-19 vaccination stimulates antigen-presenting cells (APCs), eliciting innate and subsequent adaptive immune responses. The first hypothesis for the development of IgAN in patients is the production of multiple antiglycan antibodies that cross-react with pre-existing galactose-deficient O-glycans (Gd-IgA1, **A**). The second hypothesis is an increase in pathogenic IgA production similar to influenza vaccine (**B**). The third hypothesis is that the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein (S) acts as a superantigen, causing cytokine storms (**C**). The data indicated that the COVID-19 mRNA vaccine was effective in inducing spike antigen-specific IgA and IgG production and, after the second vaccination, elicited strong CD4+ T-cell and CD8+ T-cell responses and a strong antibody response. The CD4+ T-cell response is mainly of helper T-cell type 1, producing IFN-c, TNF-α and IL-2. The main responses of CD8+ T cells are IFN-γ and TNF.

Prognosis

Currently, patients with IgA nephropathy in newly diagnosed and relapsed glomerular disease after COVID-19 vaccination have a better prognosis. Most IgAN cases with GH can spontaneously recover in a short period of time without intervention or with renin–angiotensin–aldosterone system inhibition intervention. The Gd-IgA1 and antibody titers in the patients decreased, returning the disease to a silent state. The median remission time was 6 (2–45) days. In contrast to such cases, most patients with IgA nephropathy who presented with AKI after vaccination required steroid therapy, with a median duration of remission of 30 (7–150) days. Le *et al.* assessed risk factors for progression to renal failure in 1155 Chinese adult patients with IgAN and reported that patients with a history of GH had better renal outcomes than those without such history, AKI and proteinuria affecting kidneys and life prognosis[80].

Limitations

The new opportunity presented by COVID-19 vaccine is very good for us to explore the mechanism of IgAN reflare for the first time. This review has certain limitations. First, the patients we reported are from a single case study, and there is only a temporal association between symptom onset and COVID-19 vaccination in IgAN patients, and we are unable to infer a causal relationship between vaccine and IgAN. Second, there may be many unreported vaccine-related IgAN cases, and epidemiological investigations are lacking, so we cannot determine the true incidence of IgAN after vaccination. Third, the mechanisms that we have elucidated about the vaccine-IgAN-related association only combine hypotheses from case reports and the literature, which has not been proven. Fourth, due to the small sample size, there may be errors in our statistical analysis.

Conclusions

Although these reported cases of IgA nephropathy, the COVID-19 vaccine has already produced enormous benefits in preventing COVID-19 morbidity and mortality, and its protection far outweighs any side effects identified so far. In conclusion, the occurrence of IgAN after COVID-19 vaccination is relatively rare. If urine is routinely checked and symptoms such as hematuria and foamy urine can be detected early after vaccination, patients will benefit from timely treatment of the primary disease. Further studies are required to determine the pathogenesis, incidence of induction or recurrence, treatment response and long-term clinical outcomes IgA nephropathy after COVID-19 vaccination.

Authors' contributions

Y.M. performed data collection and wrote the manuscript. G.X. was responsible for the idea, funds and paper revision. The

authors have all read and approved the final version of the manuscript.

Funding

This study was supported by the National Natural Science Foundation of China (No. 81970583 and 82060138), the Nature Science Foundation of Jiangxi Province (No. 20202BABL206025) and the Projects in the Second Affiliated Hospital of Nanchang University (No. 2019YNLZ12008).

Conflict of interest: The authors declare that they have no conflict of interest.

References

1. Maeda K, Higashi-Kuwata N, Kinoshita N, Kutsuna S, Tsuchiya K, Hattori S-I, *et al.* Neutralization of SARS-CoV-2 with IgG from COVID-19-convalescent plasma. *Sci Rep* 2021; **11**:5563.
2. Walsh EE, Frenck RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, *et al.* Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med* 2020; **383**: 2439–50.
3. Pardi N, Hogan MJ, Naradikian MS, Parkhouse K, Cain DW, Jones L, *et al.* Nucleoside-modified mRNA vaccines induce potent T follicular helper and germinal center B cell responses. *J Exp Med* 2018; **215**:1571–88.
4. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, *et al.* An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. *N Engl J Med* 2020; **383**:1920–31.
5. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, *et al.*; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; **383**:2603–15.
6. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021; **384**:403–16.
7. Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, *et al.* Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 vaccine. *N Engl J Med* 2021; **385**: 2348–60.
8. Bomback AS, Kudose S, D'Agati VD. De novo and relapsing glomerular diseases after COVID-19 vaccination: what do we know so far? *Am J Kidney Dis* 2021; **78**:477–80.
9. Gillion V, Jadoul M, Demoulin N, Aydin S, Devresse A. Granulomatous vasculitis after the AstraZeneca anti-SARS-CoV-2 vaccine. *Kidney Int* 2021; **100**:706–7.
10. Komaba H, Wada T, Fukagawa M. Relapse of minimal change disease following the Pfizer-BioNTech COVID-19 vaccine. *Am J Kidney Dis* 2021; **78**:469–70.
11. Holzworth A, Couchot P, Cruz-Knight W, Brucculeri M. Minimal change disease following the Moderna mRNA-1273 SARS-CoV-2 vaccine. *Kidney Int* 2021; **100**:463–4.
12. Sekar A, Campbell R, Tabbara J, Rastogi P. ANCA glomerulonephritis after the Moderna COVID-19 vaccination. *Kidney Int* 2021; **100**:473–4.
13. Lai KN, Tang SCW, Schena FP, Novak J, Tomino Y, Fogo AB, et al IgA nephropathy. *Nat Rev Dis Primers* 2016; **2**:16001.
14. Niel O, Florescu C. IgA nephropathy presenting as rapidly progressive glomerulonephritis following first dose of COVID-19 vaccine. *Pediatr Nephrol* 2022; **37**:461–2.
15. Abdel-Qader DH, Hazza Alkhatatbeh I, Hayajneh W, Annab H, Al Meslamani AZ, Elmusa RA, *et al.* IgA nephropathy in a pediatric patient after receiving the first dose of Pfizer-BioNTech COVID-19 vaccine. *Vaccine* 2022; **40**:2528–30.
16. Okada M, Kikuchi E, Nagasawa M, Oshiba A, Shimoda M. An adolescent girl diagnosed with IgA nephropathy following the first dose of the COVID-19 vaccine. *CEN Case Rep* 2022; **11**: 376–9.
17. Fujita Y, Yoshida K, Ichikawa D, Shibagaki Y, Yazawa M. Abrupt worsening of occult IgA nephropathy after the first dose of SARS-CoV-2 vaccination. *CEN Case Rep* 2022; **11**:302–8.
18. Klomjit N, Alexander MP, Fervenza FC, Zoghby Z, Garg A, Hogan MC, *et al.* COVID-19 vaccination and glomerulonephritis. *Kidney Int Rep* 2021; **6**:2969–78.
19. Fenoglio R, Lalloni S, Marchisio M, Oddone V, De Simone E, Del Vecchio G, *et al.* New onset biopsy-proven nephropathies after COVID vaccination. *Am J Nephrol* 2022; **53**:325–6.
20. Anderegg MA, Liu M, Saganas C, Montani M, Vogt B, Huynh-Do U, *et al.* De novo vasculitis after mRNA-1273 (Moderna) vaccination. *Kidney Int* 2021; **100**:474–6.
21. Lo WK, Chan KW. Gross haematuria after mRNA COVID-19 vaccination in two patients with histological and clinical diagnosis of IgA nephropathy. *Nephrology (Carlton)* 2022; **27**: 110–1.
22. Hanna C, Herrera Hernandez LP, Bu L, Kizilbash S, Najera L, Rheault MN, *et al.* IgA nephropathy presenting as macroscopic hematuria in 2 pediatric patients after receiving the Pfizer COVID-19 vaccine. *Kidney Int* 2021; **100**:705–6.
23. Abramson M, Mon-Wei Yu S, Campbell KN, Chung M, Salem F. IgA nephropathy after SARS-CoV-2 vaccination. *Kidney Med* 2021; **3**:860–3.
24. Tan HZ, Tan RY, Choo JCJ, Lim CC, Tan CS, Loh AHL, *et al.* Is COVID-19 vaccination unmasking glomerulonephritis? *Kidney Int* 2021; **100**:469–71.
25. Leong LC, Hong WZ, Khatri P. Reactivation of minimal change disease and IgA nephropathy after COVID-19 vaccination. *Clin Kidney J* 2022; **15**:569–70.
26. Park K, Miyake S, Tai C, Tseng M, Andeen NK, Kung VL, *et al.* Letter regarding: 'A case of gross hematuria and IgA nephropathy flare-up following SARS-CoV-2 vaccination'. *Kidney Int Rep* 2021; **6**:2246–7.
27. Lim J-H, Kim M-S, Kim Y-J, Han M-H, Jung H-Y, Choi J-Y, *et al.* New-onset kidney diseases after COVID-19 vaccination: a case series. *Vaccines (Basel)* 2022; **10**:302.
28. Kudose S, Friedmann P, Albajrami O, D'Agati VD. Histologic correlates of gross hematuria following Moderna COVID-19 vaccine in patients with IgA nephropathy. *Kidney Int* 2021; **100**:468–9.
29. Horino T, Sawamura D, Inotani S, Ishihara M, Komori M, Ichii O, *et al.* Newly diagnosed IgA nephropathy with gross haematuria following COVID-19 vaccination. *QJM* 2022; **115**:28–9.
30. Srinivasan V, Geara AS, Han S, Hogan JJ, Coppock G. Need for symptom monitoring in IgA nephropathy patients post COVID-19 vaccination. *Clin Nephrol* 2022; **97**:193–4.
31. Morisawa K, Honda M. Two patients presenting IgA nephropathy after COVID-19 vaccination during a follow-up for asymptomatic hematuria. *Pediatr Nephrol* 2022; **37**:1695–6.
32. Nihei Y, Kishi M, Suzuki H, Koizumi A, Yoshida M, Hamaguchi S, *et al.* IgA nephropathy with gross hematuria following COVID-19 mRNA vaccination. *Intern Med* 2022; **61**: 1033–7.
33. Mokos M, Bašić-Jukić N. IgA nephropathy following SARS-CoV-2 vaccination in a renal transplant recipient with a

history of aristolochic acid nephropathy. *Ther Apher Dial* 2022; **26**:667–8.
34. Alonso M, Villanego F, Segurado Ó, Vigara LA, Orellana C, Quiros P, *et al.* [De novo IgA nephropathy in a kidney transplant recipient after SARS-CoV-2 vaccination]. *Nefrologia* 2021. doi: 10.1016/j.nefro.2021.11.002.
35. Yokote S, Ueda H, Shimizu A, Okabe M, Yamamoto K, Tsuboi N, *et al.* IgA nephropathy with glomerular capillary IgA deposition following SARS-CoV-2 mRNA vaccination: a report of three cases. *CEN Case Rep* 2022; 1–7.
36. Uchiyama Y, Fukasawa H, Ishino Y, Nakagami D, Kaneko M, Yasuda H, *et al.* Sibling cases of gross hematuria and newly diagnosed IgA nephropathy following SARS-CoV-2 vaccination. *BMC Nephrol* 2022; **23**:216.
37. Perrin P, Bassand X, Benotmane I, Bouvier N. Gross hematuria following SARS-CoV-2 vaccination in patients with IgA nephropathy. *Kidney Int* 2021; **100**:466–8.
38. Horino T. IgA nephropathy flare-up following SARS-CoV-2 vaccination. *QJM* 2021; **114**:735–6.
39. Negrea L, Rovin BH. Gross hematuria following vaccination for severe acute respiratory syndrome coronavirus 2 in 2 patients with IgA nephropathy. *Kidney Int* 2021; **99**:1487.
40. Rahim SEG, Lin JT, Wang JC. A case of gross hematuria and IgA nephropathy flare-up following SARS-CoV-2 vaccination. *Kidney Int* 2021; **100**:238.
41. Plasse R, Nee R, Gao S, Olson S. Acute kidney injury with gross hematuria and IgA nephropathy after COVID-19 vaccination. *Kidney Int* 2021; **100**:944–5.
42. Watanabe S, Zheng S, Rashidi A. IgA nephropathy relapse following COVID-19 vaccination treated with corticosteroid therapy: case report. *BMC Nephrol* 2022; **23**:135.
43. Udagawa T, Motoyoshi Y. Macroscopic hematuria in two children with IgA nephropathy remission following Pfizer COVID-19 vaccination. *Pediatr Nephrol* 2022; **37**:1693–4.
44. Schaubschlager T, Rajora N, Diep S, Kirtek T, Cai Q, Hendricks AR, *et al.* De novo or recurrent glomerulonephritis and acute tubulointerstitial nephritis after COVID-19 vaccination: A report of six cases from a single center. *Clin Nephrol* 2022; **97**: 289–97.
45. Martinez Valenzuela L, Oliveras L, Gomà M, Quiros E, Antón-Pámpols P, Gómez-Preciado F, *et al.* Th1 cytokines signature in 2 cases of IgA nephropathy flare after mRNA-based SARS-CoV-2 vaccine: exploring the pathophysiology. *Nephron* 2022; 1–9.
46. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. *Kidney Int* 2004; **66**:920–3.
47. Lai KN. Pathogenesis of IgA nephropathy. *Nat Rev Nephrol* 2012; **8**:275–83.
48. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, *et al.* The pathophysiology of IgA nephropathy. *J Am Soc Nephrol* 2011; **22**:1795–803.
49. Mestecky J, Raska M, Julian BA, Gharavi AG, Renfrow MB, Moldoveanu Z, *et al.* IgA nephropathy: molecular mechanisms of the disease. *Annu Rev Pathol* 2013; **8**:217–40.
50. Bunker JJ, Erickson SA, Flynn TM, Henry C, Koval JC, Meisel M, *et al.* Natural polyreactive IgA antibodies coat the intestinal microbiota. *Science* 2017; **358**:eaan6619.
51. Gesualdo L, Di Leo V, Coppo R. The mucosal immune system and IgA nephropathy. *Semin Immunopathol* 2021; **43**:657–68.
52. Zheng N, Fan J, Wang B, Wang D, Feng P, Yang Q, *et al.* Expression profile of BAFF in peripheral blood from patients of IgA nephropathy: correlation with clinical features and Streptococcus pyogenes infection. *Mol Med Rep* 2017; **15**: 1925–35.
53. Macpherson AJ, Gatto D, Sainsbury E, Harriman GR, Hengartner H, Zinkernagel RM, *et al.* A primitive T cell-independent mechanism of intestinal mucosal IgA responses to commensal bacteria. *Science* 2000; **288**:2222–6.
54. Kiryluk K, Novak J. The genetics and immunobiology of IgA nephropathy. *J Clin Invest* 2014; **124**:2325–32.
55. McCarthy DD, Chiu S, Gao Y, Summers-deLuca LE, Gommerman JL. BAFF induces a hyper-IgA syndrome in the intestinal lamina propria concomitant with IgA deposition in the kidney independent of LIGHT. *Cell Immunol* 2006; **241**:85–94.
56. Yu H-H, Chu K-H, Yang Y-H, Lee J-H, Wang L-C, Lin Y-T, *et al.* Genetics and immunopathogenesis of IgA nephropathy. *Clin Rev Allergy Immunol* 2011; **41**:198–213.
57. Muto M, Manfroi B, Suzuki H, Joh K, Nagai M, Wakai S, *et al.* Toll-like receptor 9 stimulation induces aberrant expression of a proliferation-inducing ligand by tonsillar germinal center B cells in IgA nephropathy. *J Am Soc Nephrol* 2017; **28**:1227–38.
58. Li W, Peng X, Liu Y, Liu H, Liu F, He L, *et al.* TLR9 and BAFF: their expression in patients with IgA nephropathy. *Mol Med Rep* 2014; **10**:1469–74.
59. Makita Y, Suzuki H, Kano T, Takahata A, Julian BA, Novak J, et al TLR9 activation induces aberrant IgA glycosylation via APRIL- and IL-6-mediated pathways in IgA nephropathy. *Kidney Int* 2020; **97**:340–9.
60. Ji L, Chen X, Zhong X, Li Z, Yang L, Fan J, *et al. Astragalus membranaceus* up-regulate Cosmc expression and reverse IgA dys-glycosylation in IgA nephropathy. *BMC Complement Altern Med* 2014; **14**:195.
61. Qin W, Zhong X, Fan JM, Zhang YJ, Liu XR, Ma XY, *et al.* External suppression causes the low expression of the Cosmc gene in IgA nephropathy. *Nephrol Dial Transplant* 2008; **23**:1608–14.
62. Fellström BC, Barratt J, Cook H, Coppo R, Feehally J, de Fijter JW, *et al.*; NEFIGAN Trial Investigators. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet* 2017; **389**:2117–27.
63. Barratt J, Rovin BH, Cattran D, Floege J, Lafayette R, Tesar V, et al; NefIgArd Study Steering Committee. Why target the gut to treat IgA nephropathy? *Kidney Int Rep* 2020; **5**:1620–4.
64. Wisnewski AV, Campillo Luna J, Redlich CA. Human IgG and IgA responses to COVID-19 mRNA vaccines. *PLoS One* 2021; **16**: e0249499.
65. Arunachalam PS, Scott MKD, Hagan T, Li C, Feng Y, Wimmers F, *et al.* Systems vaccinology of the BNT162b2 mRNA vaccine in humans. *Nature* 2021; **596**:410–6.
66. Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, *et al.*; mRNA-1273 Study Group. Antibody persistence through 6 months after the second dose of mRNA-1273 vaccine for Covid-19. *N Engl J Med* 2021; **384**:2259–61.
67. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, *et al.* COVID-19 vaccine BNT162b1 elicits human antibody and T(H)1 T cell responses. *Nature* 2020; **586**:594–9.
68. Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Viant C, Gaebler C, *et al.* Enhanced SARS-CoV-2 neutralization by dimeric IgA. *Sci Transl Med* 2021; **13**:eabf1555.
69. Sterlin D, Mathian A, Miyara M, Mohr A, Anna F, Claër L, *et al.* IgA dominates the early neutralizing antibody response to SARS-CoV-2. *Sci Transl Med* 2021; **13**:eabd2223.
70. Endoh M, Suga T, Miura M, Tomino Y, Nomoto Y, Sakai H, et al In vivo alteration of antibody production in patients with IgA nephropathy. *Clin Exp Immunol* 1984; **57**:564–70.

71. van den Wall Bake AW, Beyer WE, Evers-Schouten JH, Hermans J, Daha MR, Masurel N, *et al*. Humoral immune response to influenza vaccination in patients with primary immunoglobulin A nephropathy. An analysis of isotype distribution and size of the influenza-specific antibodies. *J Clin Invest* 1989; **84**:1070–5.
72. Fischer ASL, Møller BK, Krag S, Jespersen B. Influenza virus vaccination and kidney graft rejection: causality or coincidence. *Clin Kidney J* 2015; **8**:325–8.
73. Kudose S, Batal I, Santoriello D, Xu K, Barasch J, Peleg Y, *et al*. Kidney biopsy findings in patients with COVID-19. *J Am Soc Nephrol* 2020; **31**:1959–68.
74. Premkumar L, Segovia-Chumbez B, Jadi R, *et al*. The receptor binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients. *Sci Immunol* 2020; **5**:eabc8413.
75. Stamatatos L, Czartoski J, Wan Y-H, Homad LJ, Rubin V, Glantz H, *et al*. mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection. *Science* 2021; **372**:1413–8.
76. Bradshaw PC, Seeds WA, Miller AC, Mahajan VR, Curtis WM. COVID-19: proposing a ketone-based metabolic therapy as a treatment to blunt the cytokine storm. *Oxid Med Cell Longev* 2020; **2020**:6401341.
77. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, *et al*. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg Microbes Infect* 2020; **9**:1123–30.
78. Sattler A, Schrezenmeier E, Weber UA, Potekhin A, Bachmann F, Straub-Hohenbleicher H, *et al*. Impaired humoral and cellular immunity after SARS-CoV-2 BNT162b2 (tozinameran) prime-boost vaccination in kidney transplant recipients. *J Clin Invest* 2021; **131**:e150175.
79. Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L, *et al*. Low immunization rates among kidney transplant recipients who received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine. *Kidney Int* 2021; **99**:1498–500.
80. Le W, Liang S, Hu Y, Deng K, Bao H, Zeng C, *et al*. Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. *Nephrol Dial Transplant* 2012; **27**:1479–85.