variants in human genetic disease. Pathway-specific models of podocytopathies and FSGS such as this also highlight the potential in using simpler genetic systems, such as the fly or the zebrafish, as discovery platforms to screen patient-specific therapies for FSGS.

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AUTHOR CONTRIBUTIONS

I.A. Drummond wrote the original draft.

REFERENCES


mRNA COVID-19 Vaccines and Their Risk to Induce a Relapse of Glomerular Diseases

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Worldwide, vaccination against severe acute respiratory syndrome coronavirus 2 has reduced the case fatality rate of coronavirus disease 2019 (COVID-19) in patients with kidney disease,1 but vaccination hesitancy remains a problem for various reasons. In patients with glomerular disease, there is the concern that vaccination may trigger a relapse of disease activity and a further decline in residual kidney function. In the absence of reliable data, advising patients on the individual risks and benefits has been challenging. Up until January 2022, numerous case reports and series reported 40 relapses of glomerulonephritis, kidney vasculitis, or podocytopathies in a temporal association with a coronavirus vaccine.2 Minimal change disease (MCD) relapsed preferentially after the first vaccine dose, whereas other entities relapsed after the second or third dose.2 However, in data on the background incidence of glomerular disease in nonvaccinated controls of the same population, the role of the vaccine as a trigger of a relapse has remained questionable.

In this issue of JASN, Canney et al. report data from a British Columbia Canadian clinical and pathology registry, which followed a large sample of 1105 patients with glomerulonephritis, kidney vasculitis, and podocytopathies from December 14, 2020, to September 21, 2021. The study aimed to investigate whether the rollout of COVID-19 vaccines affect the relapse risk of these disease entities. Most patients received a mRNA vaccine (67% BNT162b2, 30% mRNA-1273), with the remainder (3%) receiving ChAdOx1. During this period, they defined a disease relapse as an increase of serum

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creatinine and proteinuria. A total of 134 (12.1%) patients experienced a relapse during the 281 days of follow-up. Among these, 24 relapses were considered as vaccine-associated relapses, defined as relapses occurring within a period of 30 days after vaccine administration. Overall, the authors found no increase of disease relapse after the first dose of COVID-19 vaccine administration (hazard ratio 0.65; 95% confidence interval, 0.32 to 1.32) but a two-fold increase after subsequent doses (hazard ratio 2.16; 95% confidence interval, 1.03 to 4.51). The risk of a disease flare during 210 days of follow-up in the absence of COVID-19 vaccine exposure ranged from 6% in membranous nephropathy (MN) to 19% in lupus nephritis (LN). The absolute risk after administration of a second or third vaccine dose of developing a disease relapse varied from 1%–2% in ANCA-associated vasculitis, MCD, MN, and FSGS to 3%–5% in IgA nephropathy and LN. Further sensitivity analysis extending the time period to 45 days after vaccination (see Figure 1) and restriction analysis to patients who received at least one vaccine (92% of the cohort) or two vaccines (89%) confirmed the association of glomerular disease relapse with administration of a second or third vaccine dose.3

There are several limitations of the work presented by Canney et al. The registry did not capture hematuria, which may be dispensable in podocytopathies but would add to specificity for a relapse of glomerulonephritis and kidney vasculitis. A survey in Japan identified 27 cases presenting with gross hematuria after COVID-19 vaccination. Among the 27 patients, only four underwent a kidney biopsy, and only one relapse was associated with an increase in serum creatinine. Gross hematuria usually occurs within the first days after vaccination, and usually resolves without specific therapy. These findings could imply that Canney et al. might have missed some relapses of glomerulonephritis, which anyway may have consequences for future kidney function decline. In the report by Canney et al., none of the 24 patients with a recurrence of glomerular disease after COVID-19 vaccination required a kidney biopsy, and only four (17%) of the patients had a change in immunosuppression, defined by a changing pattern in prescription. This again argues that most of the disease relapses were mild in nature, although their long-term effect on kidney function decline would warrant further follow-up. Notably, only three patients received a third vaccine dose because administration of booster doses was uncommon during the study period, whereas many countries are now offering fifth and sixth doses to vaccine recipients.

![Figure 1. A total of 1105 patients with established glomerulonephritis were followed in the registry. Most patients received two doses of COVID-19 vaccines. Relapses occurred in 134 patients during a follow-up period of 281 days, of whom 24 had a relapse within 30 days of vaccine administration. There is an increased risk after administration of the second or third dose of COVID-19 vaccine administration, and a minimal increased absolute risk for all entities studied. The histopathology picture was kindly provided by Dr. Victoria Bardsley (Department of Pathology, Addenbrooke’s Hospital, Cambridge, United Kingdom) and shows active necrosis in a patient with established ANCA-GN undergoing kidney biopsy 24 days after her fourth vaccine dose. IgAN, IgA nephropathy.](image-url)
immunocompromised patients. Subanalysis investigating differences between approved mRNA vaccines (BNT162b2 versus mRNA-1273) would provide important information because mRNA-1273 elicits a better humoral vaccine response, without increasing the rate of side effects and thus presumably also the risk of disease flare-ups.

The work by Canney et al. highlights that disease relapses after mRNA COVID-19 vaccines are infrequent and that most of these disease relapses are self-limiting without a need to perform a repeat kidney biopsy or modification of immunosuppression. This is important information when discussing the pros and cons of vaccination with our patients, and it increases confidence in stating that mRNA vaccines are safe to use in most patients. COVID-19 vaccines are effective, even in immunosuppressed individuals. Analysis of the VISION network reported a vaccine effectiveness against hospitalization in the pre-Omicron era of 77% versus 90%. Reduced vaccine responses are reported in patients with ongoing “high-dose” immunosuppression, namely higher doses of steroids, alkylating agents, rituximab, mycophenolate mofetil, or calcineurin inhibitors, and in the absence of a humoral response or a low antibody response to prior COVID-19 vaccines, further booster doses, ideally with the adapted bivalent mRNA vaccines, should be offered. There is a clear benefit to vaccination in individuals with glomerular diseases because these patients often have worsening of kidney function, higher frequencies of severe forms of COVID-19, and reduced viral clearance, leading to prolonged days of hospitalization.

However, there is limited information about the use of a third and fourth vaccine doses, which are now regularly recommended to patients with glomerular disorders. Repetitive stimulation of the immune system may further increase the frequency of disease relapses, and the cumulative risk upon several vaccine doses may reach a higher degree of clinical significance. Even with this study, we remain with this uncertainty—whether patients with a disease relapse after a COVID-19 vaccine will develop further relapses when subsequent doses are administered. The latter scenario seems likely, and prevaccine administration of low-dose immunosuppression (i.e., steroids) might be considered in such cases. Potential differences in relapse risk between mRNA and viral-vectorized vaccines remain to be clarified.

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AUTHOR CONTRIBUTIONS

H.-J. Anders was responsible for supervision and reviewed and edited the manuscript, and A. Kronbichler was responsible for conceptualization and wrote the original draft of the manuscript.

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Kidney transplantation is mired in mediocrity. Acceptance of current outcomes thwarts innovation; over the past two decades there has been no significant improvement in long-term allograft survival or approval of new immunosuppressant drugs. A barrier to progress is our limited understanding of disease processes that lead to allograft failure on the basis of descriptive histology alone. Novel molecular diagnostics provide powerful new tools to potentially understand complex disease processes. At the XV Banff conference for allograft pathology, a major step was taken to accelerate the use of molecular diagnostics in allograft pathology: the introduction of the Banff Human Organ Transplant (B-HOT) gene panel, which includes nearly 800 genes expressed in the most common histologic diagnoses encountered in clinical practice. To promote the use of the B-HOT panel, a partnership with NanoString Technologies was established. This technology allows multiplex transcript quantification from formalin-fixed, paraffin-embedded biopsy samples that is paired with analytical software and allows individual laboratories to integrate the technology into clinical workflows. To enable multicenter validation, a data integration platform was created with an initial goal of analyzing B-HOT transcripts in ≥1000 clinical biopsy samples.

In this issue of JASN, Rosales and colleagues provide the first report of work related to the Banff group’s bold vision. In this retrospective analysis of 326 archived biopsy specimens enriched for chronic active antibody-mediated rejection (CAMR; n=120) and T cell–mediated rejection (TCMR; n=49) obtained an average of 4 years post-transplant, the authors correlated Banff histopathology scores with B-HOT gene transcripts. The B-HOT panel distinguished CAMR or TCMR in aggregate using AMR and TCMR gene sets identified and validated in earlier microarray studies. The investigators hypothesized pathogenic insights would be revealed by correlation of AMR gene expression pathway scores with individual Banff histologic findings. Only one Banff pathology lesion, peritubular capillaritis, was correlated with AMR pathways in CAMR. Glomerular inflammation did not correlate strongly with AMR scores and there was no correlation of C4d or other Banff scores with AMR scores in the CAMR diagnostic group. Graft failure in patients with CAMR or borderline/suspicious TCMR was associated with multiple damage pathways, confirming previous observations that damage, rather than AMR pathway activity, was more relevant to CAMR outcome. Patients with multiple biopsy specimens without CAMR on the initial biopsy sample, but who developed CAMR on a subsequent biopsy sample within 5 years, showed elevation of a ten-gene set associated with donor-specific antibodies, suggesting CAMR might be predicted by molecular transcripts far earlier than histologic CAMR.

The study demonstrates the potential and challenges of the Banff group’s approach. Investigators are now able to perform transcriptomic, proteomic, and metabolomic analysis that can provide information at the cellular and subcellular level, in addition to microscopic review. To date, most transcriptomic studies have used homogenized tissue or pooled samples obtained from microdissection studies. These seminal studies have identified groups of genes within molecular pathways that associate with specific Banff histologic findings. The disadvantages of microarrays include loss of anatomic localization, which precludes “histomolecular integration,” the requirement for a dedicated biopsy sample, an inability to examine archived samples, and limited feasibility to integrate the technology into routine clinical practice because of cost and the requirement to ship samples to a commercial reference laboratory.

In situ techniques, such as NanoString, have the potential to overcome many of these issues but also have important limitations. The ability to analyze only a limited number of genes inherently constrains understanding of disease processes to known genes and established mechanistic pathways. The confirmation that B-HOT genes differentiate TCMR and CAMR in the Rosales et al.’s study is anticipated and self-fulfilling because the examined genes are limited to those already associated with these findings in microarray studies. An in silico assessment of the B-HOT gene panel used three bioinformatic