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EDITORIAL

Buyer beware: The risks of donor-derived vaccine-induced thrombosis and thrombocytopenia

The emergence of the Sars-CoV-2 virus has posed unique challenges specific to transplantation and donation. For our transplant patients in our waiting lists, they have faced uncertainty, unsure if the pandemic will delay live-saving transplants. In March 2021, vaccine-induced thrombosis and thrombocytopenia (VITT) and central venous sinus thrombosis were recognized first in Europe with the Astra-Zeneca ChAdOx01 nCoV-19 vaccine and then in the United States with the Janssen Covid-19 Ad.26.COV2.S vaccine. Not only did this represent a new risk to describe to our patients and colleagues, but because of the life-threatening nature of this complication, we began receiving offers from donors who had died from VITT.[1,2]

In this issue of the *American Journal of Transplantation*, we note reports from both Greenhall and Ushiro-Lumb et al. and Loupy et al., contrasting recent European experience with vaccinated organ donors, who tragically died from VITT.[3,4] Mechanistically, our understanding of VITT is evolving with a recent *Nature* paper highlighting key features–it resembles heparin-induced thrombocytopenia (HIT) in that it is associated with platelet-activating antibodies against platelet factor 4 (PF4).[5] In contrast to HIT, however, patients with VITT develop thrombosis and thrombocytopenia without heparin exposure. Antibodies formed after vaccination mimic heparin by tightly binding to a similar site on PF4, creating PF4 tetramers and inducing complexes to cascade and cluster, generating thrombosis via FcγRIIa-dependent platelet activation.

Greenhall, Ushiro-Lumb, and colleagues describe the early United Kingdom experience reviewing 13 consented organ donors, who suffered VITT following recent administration of the ChAdOx01 nCoV-19 vaccine. Ten donors proceeded to donate 27 organs to 26 recipients. The donors were young, with a median age of just 34 years, and 85% were female. The average time from vaccination to hospital admission was just 10 days. Critically, 92% suffered from intracranial hemorrhage. Cerebral venous sinus thrombosis and extra-cranial thrombosis occurred in 54% and 46% respectively.

Recipients fared worse than expected. Three recipients developed early allograft failure—in two livers and one kidney—requiring emergent explanation. Additionally, a further two kidneys had delayed graft function, and in total, six recipients suffered major thrombotic or hemorrhagic postoperative complications. Intriguingly, 3 out of 13 recipients tested had anti-PF4 antibodies appear, suggesting a possible transmission of either passive antibodies or pathogenic donor lymphocytes, or at the very least, the de novo development of antibodies posttransplant. After median 19 days of follow-up, only 78% of the allografts retained satisfactory function.

Loupy et al. present a review of five French donors who died as a result of central venous sinus thrombosis and VITT secondary to the ChAdOx01 nCoV-19 vaccine. Similar to the UK experience, the median duration from vaccination to ICU admission was just 13 days, and extracranial thrombosis noted at procurement was so severe result in some organs being declined. After careful consideration, 10 organs (one liver, one lung, two hearts, and six kidneys) were ultimately transplanted into nine recipients. At a median follow-up of 52 days, all were doing well, although a thrombectomy was needed for the lung recipient. No recipient developed graft failure or significant allograft dysfunction.

It is certainly possible that early organ damage in these donors was occurring prior to procurement, and potential differences in donor management between the two cohorts—for example, anticoagulation—were not discussed. Consequently, Organ Procurement Organizations (OPO), and recipient transplant centers should have a low threshold to biopsy organs from donors dying of possible VITT, to look for microvascular thrombosis, prior to final acceptance. As noted, this is now part of national policy in France and may have led to earlier identification of at-risk allografts in their cohort.

There are no published case reports of transplant programs using organ donors with VITT secondary to the Janssen vaccine, which has been the adenovirus vector vaccine used in the United States. In general, however, the risks of VITT from the different adenovector vaccines appear similar.[6,7] On the surface, such a donor would be appealing: they are typically younger and with lower rates of chronic disease. Given the terminal event is usually a catastrophic central nervous system thrombosis or hemorrhage, potential donors with VITT generally have short hospital exposures and therefore less risk for active hospital-acquired infection at the time of procurement.

Yet "buyer beware"! Taken together, the reports in the journal demonstrate the ability for major and devastating impacts on the affected organ and recipients. Transplant centers and OPOs, mindful of the spectrum of VITT disease, could make use of organ biopsy, where possible, to fully evaluate the quality of the organ and examine if microvascular thrombosis is present. Furthermore, given organ damage may evolve after implantation, centers noting early and unexpected

thrombocytopenia in their recipient may benefit from checking anti-PF4 antibodies. Given the mechanism of cascading anti-PF4 binding, and the parallels to HIT, recipients of such organs may need early evaluation for alternative anticoagulation strategies, given heparin-based products accelerate the thrombosis and thrombocytopenic risk.

So, should we accept or not accept organs from donors with VITT? As with all deceased donor organs, these decisions are based on risk versus benefit for the recipient. Significant caution is advised but a blanket moratorium on donors with VITT is not presently indicated. Recipient centers should be allowed and in fact encouraged to gauge the risk of different donors against the clinical urgency of patients on their waitlist. That flexibility is important. But if a center is to now accept organs from a donor who died due to complications of VITT, a robust consent process describing the potential risks and a more cautious organ evaluation now seems appropriate.

Finally, both research teams presenting in the journal should be commended—they have rapidly disseminated critical and ominous information in the heat of a pandemic. It is a measure of their national reporting structures that they can gather important data across multiple centers so quickly. Such diligence is absolutely crucial as we continue to learn and evolve with SARS-CoV-2 and continue to advocate for the best outcomes for our transplant recipients.

KEYWORDS

donors and donation: donor evaluation, editorial/personal viewpoint, infectious disease, organ acceptance, organ procurement and allocation, organ transplantation in general

DISCLOSURE

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available.

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