TLT development in patients with or without rituximab treatment being comparable.

In conclusion, we think our study documents that advanced stage II TLTs are associated with progressive graft dysfunction, independent of interstitial inflammation.

DISCLOSURES

M. Yanagita reports receiving research funding from Boehringer Ingelheim and Tanabe Mitsubishi; reports receiving honoraria from Astellas, Chugai, Kyowa Kirin, and others for lectures; and reports having other interests/relationships with the International Society of Nephrology and the Japanese Society of Nephrology. J. Floege reports having consultancy agreements with AstraZeneca, Bayer, Calliditas, Idorsia, Novartis, Omeros, and Traverce; and reports receiving honoraria from AstraZeneca, Bayer, Calliditas, Fresenius, Idorsia, Novartis, Omeros, Traverce, and Vifor. All remaining authors have nothing to disclose.

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SARS-CoV-2 Vaccination in Kidney Transplant Recipients: Should We Consider Intradermal Vaccination?

Schrenzenmeier and colleagues report a poor effect of a third dose of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in kidney transplant recipients (KTR) who had no response to the two previous doses (December 2021 issue).1 At 27 days after the third dose, seroconversion was observed in only nine of the 25 (36%) KTR without a previous seroconversion. This low efficacy of booster doses in KTR emphasizes the need for alternative multidose vaccination strategies for transplant recipients and, more broadly, patients who are immunocompromised. Moreover, coronavirus disease 2019 vaccines are still scarce worldwide and a vast majority of the world’s population is still awaiting their first jab. The World Health Organization advises prioritizing global vaccination coverage, and preserving booster doses for the populations in greatest need.2 To address these two issues, we feel that intradermal administration should be considered in patients who are immunocompromised.3(preprint)

Indeed, a recent report on 38 healthy adults provides preliminary evidence that intradermal injection of SARS-CoV-2 mRNA vaccines is as effective as intramuscular injection.3(preprint) Intradermal SARS-CoV-2 mRNA vaccination (n = 24) resulted in equal antibody responses compared with intramuscular vaccination (n = 14), using only one fifth to one tenth of the intramuscular dose. The efficacy of the intradermal dose is in line with previous studies on influenza vaccine responses in patients who are nonresponding after kidney transplant, showing significantly greater seroconversion rates and significantly higher peak antibody titers after intradermal booster vaccination compared with intramuscular administration.4 Therefore, intradermal SARS-CoV-2 vaccination has the potential to solve both the scarcity of vaccines at a global level, and to improve efficacy. Studies investigating the clinical efficacy of dose-sparing intradermal SARS-CoV-2 booster vaccines are urgently needed.

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### Authors’ Reply: SARS-CoV-2 Vaccination in Kidney Transplant Recipients: Should We Consider Intradermal Vaccination?

We appreciate the comment of Wijtvliet and colleagues and fully agree that low efficacy of coronavirus disease 2019 vaccinations in kidney transplant recipients (KTRs) represents a major problem and that new vaccination strategies are urgently needed. Intradermal application of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines is an interesting approach because first data from healthy adults suggest robust serological response at lower doses. However, limitations of the intradermal delivery trial are the small sample size and the lack of analysis of the cellular immune response. Therefore, broader clinical studies in healthy individuals and KTRs are necessary to assess long-term clinical efficacy. Thus, much more data are needed to recommend intradermal application of mRNA-based vaccines against SARS-CoV-2.

The intriguing pathophysiological idea behind the preliminary report in medRxiv that Wijtvliet et al. reference is that more antigen-presenting cells reside in the skin than in skeletal muscle, thereby raising a stronger vaccine response with a lower dose. Although previous data from influenza vaccination suggest a better response of intradermal application in KTRs, it is not clear how the data can translate to mRNA vaccines, which elicit an excellent immediate immune response in most individuals. Our data demonstrate that KTRs develop high frequencies of antigen-specific CD4 cells after vaccination, suggesting successful antigen presentation. In KTRs the mature immune response, which requires cellular proliferation and a complex interplay among immune cells, seems to be blocked by immunosuppressants. To directly address this problem, we have very recently described excellent efficacy of a fourth dose of the mRNA vaccine BNT162B2 in 29 KTRs without previous immune response under a temporary (5 weeks) hold of mycophenolate (MPA). Seroconversion rate (anti-S1-IgG and neutralizing antibodies) was 84% after 1 month and we saw a rapid increase in antigen-specific peripheral B cells.

As expected, kidney function remained unchanged because several previous studies have demonstrated the safety of this intervention and MPA cessation is standard for women who want to become pregnant. The temporary hold of MPA under adequate treatment with calcineurin inhibitor plus corticosteroids, together with close surveillance, might be the most feasible and fastest way to achieve adequate protection for KTRs, especially in light of emerging new variants.

We agree that intradermal application of a reduced dose would be one way to improve worldwide accessibility to the vaccines, especially in the face of production shortages or high costs. However, KTRs represent a very small, yet highly vulnerable, patient cohort that, despite repeated vaccination, do not contribute substantially to global misdistribution of vaccines.

### DISCLOSURES

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