Immune Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Liver Transplant Recipients

Aitor Odriozola, MD,[1] Patricia Lamadrid-Perojo, BS,[2] Antonio Cuadrado, MD, PhD,[1] David San Segundo, BS, PhD,[2] María del Barrio, MD,[1] José Ignacio Fortea, MD, PhD,[1] Angela Puente, MD, PhD,[1] Lidia Amigo, BSc,[1] Roberto Fernández-Santiago, MD, PhD,[3] Federico Castillo, MD, PhD,[3] María Achalandabaso, MD,[3] Juan Andrés Echeverri, MD, PhD,[3] Juan Carlos Rodríguez-Sanjuan, MD, PhD,[3] Marcos López-Hoyos, MD, PhD,[2] Javier Crespo, MD, PhD,[1] and Emilio Fábrega, MD, PhD[1]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination has been recommended for solid organ transplant recipients (SOTRs).[1] Unfortunately, >50% of SOTRs do not mount antibody responses after 2 full doses.[2] Consequently, SOTRs may be at risk of developing COVID-19 requiring hospital admission despite vaccination.[3] On September 7, 2021, Spanish National Authority for Health made a recommendation to administer a third vaccine dose for all SOTRs and other immunocompromised patients at least 4 wk after the second dose. For SOTRs, early reports provided encouraging evidence regarding the immunogenicity and seroconversion following a third dose, although only a minority of patients were liver transplant recipients (LTRs).[4] The aim of the work was to assess the immunogenicity of third-dose vaccination in LTRs. Here, we report the antibody responses induced to 2 dose vaccination and a subsequent third dose of the mRNA-1273 SARS-CoV-2 vaccine in 129 LTRs (**Appendix S1, SDC,** http://links.lww.com/TP/C405). The anti-SARS-CoV-2 S1 antibodies were measured by chemiluminescent microparticle immunoassay using the SARS-CoV-2 IgG II Quant assay on the Aliniti I (Abbot; Chicago, IL).[5] The median level of anti-S1 IgG after 2 doses was 3594 (interquartile range [IQR], 644–11 515) AU/mL and after the third dose increased to 29 783 (IQR, 10 726.5–40 287.5) AU/mL ($P < 0.001$) (Figure 1A). After 2 dose vaccination, seronegative, low, and high responses were observed in 16 (12.4%), 51 (39.6%), and 62 (48%) patients, respectively, whereas, after third dose, the frequency of seronegatives, low, and high responders was 4 (3.1%), 8 (6.2%), and 117 (90.7%) patients, respectively (Figure 1B).

Twelve of 16 seronegative LTRs after 2 doses produced weak antibody response after the third dose, with a median anti-S1 antibody level of 858 (IQR, 359.75–2779) AU/mL. Nonresponse after third dose was associated with mofetil mycophenolate treatment (75% versus 23.2%) ($P < 0.001$), a higher dose of this drug (1666 [SD, ±577] versus 1068 [SD, ±394] mg) ($P = 0.02$), and lower estimated glomerular filtration rate (32.3 [SD, ±17.3] versus 69.4 [SD, ±18.9] mL/min/1.73m^2) ($P = 0.001$) (**Appendix S1, SDC,** http://links.lww.com/TP/C405).

In 1 of 4 seronegatives (25%) after third dose had vaccine-specific T-cell response. The overall immune response detected after third dose was 126 of 129 (97.67%).

Our findings suggest that the third dose induces a more robust antibody response according to a protective immunity in LTRs, in agreement with data in other SOTRs.[4]

Importantly, the third dose allowed seroconversion in 75% of seronegative cases after the 2 doses schedule. In addition, patients with low response significantly increased their antibody levels. However, anti-S1 antibody titers of these patients remained below the cutoff we defined as high-responder status (4160 AU/mL).

The LTRs who did not develop anti-SARS-CoV-2 antibodies after the third dose, received higher mofetil mycophenolate dose and lower glomerular filtration, factors already identified for weak immune response.[6,7]

In conclusion, the homologous third dose reinforces the humoral SARS-CoV-2 specific immune response in almost

Received 17 December 2021. Revision received 27 February 2022.

Accepted 3 March 2022.

[1]Department of Gastroenterology and Hepatology, Marqués de Valdecilla University Hospital, IDIVAL, Clinical and Translational Digestive Research Group, University of Cantabria, Santander, Spain.

[2]Department of Immunology, Marqués de Valdecilla University Hospital, IDIVAL, Transplant and Autoimmunity Research Group, University of Cantabria, Santander, Spain.

[3]Department of General Surgery, Marqués de Valdecilla University Hospital, IDIVAL, School of Medicine, University of Cantabria, Santander, Spain.

This research was partially supported by grant from Cantabrian Government #2020 UIC22-PUB-0019 (to M.L.-H.).

The authors declare no conflicts of interest.

All authors had access to the study data and critically reviewed, revised, and approved the final article. A.O., D.S.S., E.F., J.C., M.d.B., and M.L.-H. participated in research design. A.O., D.S.S., E.F., A.C., J.C., J.I.F., A.P., L.A., R.F.-S., F.C., M.A., J.E., J.C.R.-S., and M.L.-H. participated in the performance of the research. A.C., A.O., D.S.S., E.F., J.C., J.I.F., M.L.-H., and P.L.-P. participated in the writing of the article. A.C., A.O., D.S.S., E.F., J.C., J.I.F., M.L.-H., and P.L.-P. participated in data analysis.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

Correspondence: David San Segundo, BS, PhD, Immunology Department, Marques de Valdecilla University Hospital, Avd Valdecilla 25, 39008, Santander, Cantabria, Spain. (david.sansegundo@scsalud.es).

ISSN: 0041-1337/20/1067-e341

DOI: 10.1097/TP.0000000000004147

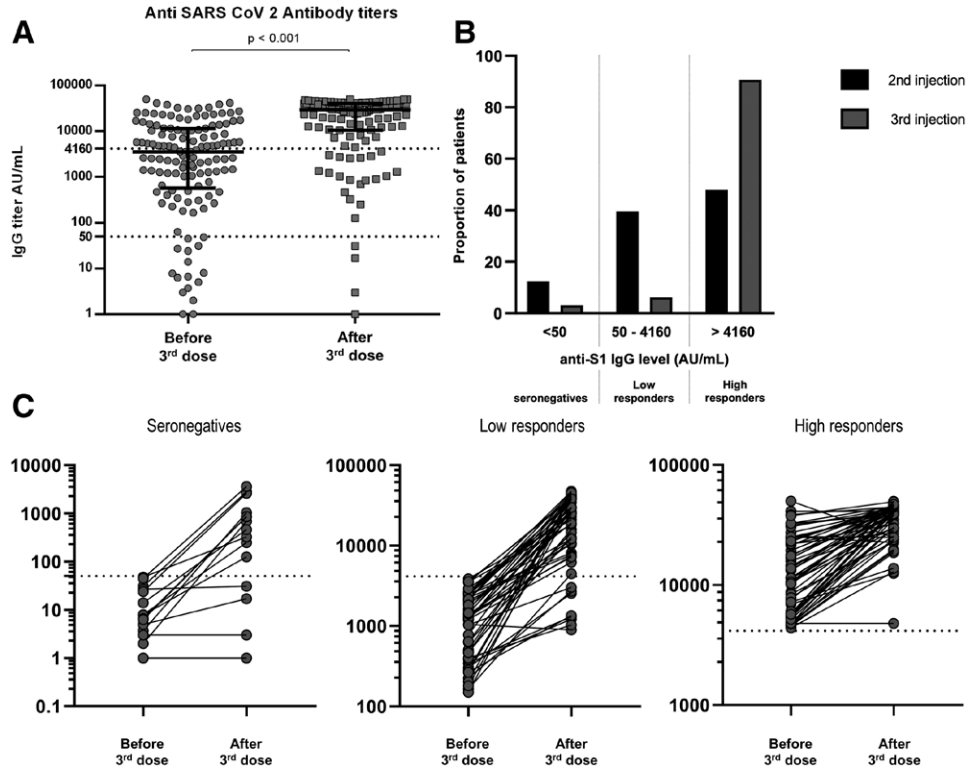

FIGURE 1. Humoral response after third-dose vaccination in liver transplant recipients: Anti-S1 IgG level after the second and third mRNA-1273 SARS-CoV-2 dose in the cohort of LTRs (A). Percentage of LTRs according to response after the second and third dose of third mRNA-1273 SARS-CoV-2 vaccine (B). Anti-S1 IgG levels after the second and third dose the of mRNA-1273 SARS-CoV-2 vaccine in (left) seronegatives, (center) low-responders, and (right panel) high-responder LTRs. Each patient is represented by 2 circles with a connecting line (C). IgG, immunoglobulin; LTR, liver transplant recipient; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

98% of LTRs. Furthermore, the cellular immune response was detectable in 1 of 4 LTRs after the third dose. Our data favor the use of a third dose in LTRs.

Limitations of this study include the observational design, the small number of patients, the absence of serial measurements between doses and after vaccination, and the lack of exploration of neutralizing antibodies. Finally, we cannot conclude that the improved humoral immunity correlates with clinical protection.

REFERENCES

1. American Society of Transplantation. Statement on COVID-19 vaccination in solid organ transplant recipients. Available at https://www.myast.org/statement-covid-19-vaccination-solid-organ-transplant-recipients. Accessed May 16, 2021.
2. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA.* 2021;325:2204–2206.
3. Wadei HM, Gonwa TA, Leoni JC, et al. COVID-19 infection in solid organ transplant recipients after SARS-CoV-2 vaccination. *Am J Transplant.* 2021;21:3496–3499.
4. Kamar N, Abravanel F, Marion O, et al. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients. *N Engl J Med.* 2021;385:661–662.
5. Chapuy-Regaud S, Miédougé M, Abravanel F, et al. Evaluation of three quantitative anti-SARS-CoV-2 antibody immunoassays. *Microbiol Spectr.* 2021;9:e0137621.
6. Del Bello A, Abravanel F, Marion O, et al. Efficiency of a boost with a third dose of anti-SARS-CoV-2 messenger RNA-based vaccines in solid organ transplant recipients. *Am J Transplant.* 2022;22:322–323.
7. Smith KG, Isbel NM, Catton MG, et al. Suppression of the humoral immune response by mycophenolate mofetil. *Nephrol Dial Transplant.* 1998;13:160–164.