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COMMENTARY

Living During COVID-19 While Immunocompromised: A Patient and Physician Perspective from France

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ABSTRACT

This article is co-authored by a kidney transplant recipient and her nephrologist. By sharing her personal experience of the coronavirus disease 2019 (COVID-19) pandemic, the patient illustrates the concerns of immunocompromised patients during this unprecedented health crisis. She describes the difficulties encountered at work, the omnipresent protective measures, and the need for appropriate information. The nephrologist, who follows a cohort of over 1700 kidney transplant recipients, recounts the medical team's struggle to protect their vulnerable patients against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a veritable succession of hopes and disappointments. She describes the management of immunosuppression in kidney transplant recipients, the deployment of the COVID-19 vaccination program with the finding of poor immune responses in many patients including those receiving immunosuppressant drugs after kidney transplant, and the first use of prophylactic monoclonal antibodies. From both the patient's and the physician's perspectives, the COVID-19 pandemic has required continuous adaptation.

PLAIN LANGUAGE SUMMARY

A kidney transplant patient and her physician describe their experiences during the coronavirus disease 2019 (COVID-19) pandemic in France. The patient outlines her ongoing challenges during the pandemic due to being on lifelong anti-rejection drugs; such treatment suppresses the immune system resulting in poor ability to fight infection and poor response to vaccination. She discusses anxieties regarding having to travel to and attend work as an individual vulnerable to COVID-19. In addition, she found it difficult to find appropriate information at the start of the pandemic. Once vaccinated, she did not develop antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). She subsequently received preventive antibody treatment which relieved her anxieties considerably. However, the pandemic is still very real for her, and she has gone from having an invisible disability—her kidney transplant—to

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having a visible disability because she always wears a mask. Thus far, she has not contracted COVID-19. The physician recounts her challenge to protect vulnerable kidney transplant patients against SARS-CoV-2, the initiation of the COVID-19 vaccination program, the finding of poor immune responses to vaccination in many patients, and the first use of antibody therapies to prevent against SARS-CoV-2 infection. In 2023–2024, the situation is much more manageable for physicians because COVID-19 is better controlled in terms of severity and management than it was in 2020–2021. The COVID-19 pandemic has required continuous adaptation from both the patient's and the physician's perspective.

Keywords: COVID-19; Immunosuppressive drug; Kidney transplant; Patient's perspective; Prophylactic monoclonal antibodies; SARS-CoV-2 vaccine

Key Summary Points

A kidney transplant recipient and her nephrologist describe their experiences during the coronavirus disease 2019 (COVID-19) pandemic.

The patient outlines her ongoing challenges due to being immunocompromised, including difficulties at work, use of protective measures, and the need for appropriate information.

The nephrologist recounts the challenge to protect immunosuppressed patients against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the initiation of the COVID-19 vaccination program, the finding of poor immune responses in many patients, and the first use of prophylactic monoclonal antibodies.

The COVID-19 pandemic has required continuous adaptation from both the patient's and the physician's perspective.

PATIENT'S PERSPECTIVE: MME ELISE FOUDRAT

I am 41 years old, and I work as a social worker in a psychiatric hospital. I have been in a relationship for 15 years and have no children. In 1998, at the age of 16, I was diagnosed with a glomerulonephritis of unknown origin following acute lung edema. My first kidney transplant, which was a living donor transplant from my father, was performed a year later when I was 17. Six years later, in 2005, when I was 23 years old, for no clear reason, the transplanted kidney stopped working and I returned to dialysis. At the age of 24, I received my second transplant, this time from a deceased donor. After a few years, I contracted an opportunistic infection, hepatitis E, which was treated with ribavirin. Of the 50 cases treated in France at the time, I was the only one for whom ribavirin failed. The graft kidney was damaged by infection or drug toxicity; 6 months later, the graft had failed and I had to return to dialysis. A year and a half later, in August 2019, I received my third transplant from a deceased donor. And 6 months later, the coronavirus disease 2019 (COVID-19) pandemic arrived.

As a recent transplant recipient, I rapidly started to feel anxious. I was reading a lot of information on doctors' and scientists' Twitter accounts, and it was clear that it was going to be a complicated time for me. At the beginning of March 2020, just before the first lockdown was imposed in France, my 6-month post-transplant follow-up ended, and I had to go back to work. At that time, I was living and working in Paris, and had to take the metro every day to go to work. My transplant medical team tried to reassure me and told me that I did not need to take any special precautions. However, at my resumption interview with the medical officer at work, I asked for filtering facepiece (FFP2) masks for my metro journeys. In the Paris metro, I was the only person wearing a mask! After only a week, I asked the medical team following my transplant to give me sick leave because I was so anxious about the health situation. Lockdown was a huge relief for me: it was actually a time that I lived through very well. During the lockdown, I

resumed working from home with shielding. In January 2021, the COVID-19 vaccination campaign had just begun in France and many people simply thought the pandemic was over. My employer asked me to return to work on-site, but I was far too anxious to do so; I could not possibly already be protected by vaccination since the campaign had only just started. Thanks to a legislative decree concerning employees vulnerable to COVID-19, I was able to continue working at home.

Less than a week after the start of the vaccination campaign, I received my first dose of COVID-19 vaccine. I had no adverse reactions to any of the doses I received. After my third dose, in the summer of 2021, a test to detect antibodies showed that I had still not developed any antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and I was not protected by the vaccine. The pandemic was still very present for me.

Despite this, I have never actually caught COVID-19. This is because I took all the necessary protective measures for three and a half years and, looking back, I think my anxiety was a good defense mechanism. My partner wore a mask in public spaces until spring 2023. Unfortunately, that has become more difficult for him in his professional life, and he finally stopped wearing it for social reasons. In my case, my fear has enabled me to detach myself from the way others look at my protective measures. In total, I have received seven doses of COVID-19 vaccine, the last in August 2023. Getting vaccinations has become more difficult. In the beginning it was easy to find a dose if you were a patient at risk, but now getting vaccinated outside the vaccination schedule has become very complicated. You need to be really quite motivated!

I first heard about a prophylactic treatment against COVID-19 on Twitter in spring 2021. In August 2021 when I asked my medical team in Paris if I could benefit from it, I was told that the hospital did not have any doses because they had been sent to Guadeloupe and Martinique in the Caribbean, which were both going through a major COVID-19 wave at the time. I moved to Strasbourg (in the Alsace region of France) a month later and was transferred to the care of Prof Sophie Caillard and her team. The new medical team told me about the prophylaxis therapy right from the start of my care pathway, and I was able to benefit from an injection of casirivimab-imdevimab very quickly because the hospital had doses available. This enabled me to return to work and start my new job in Strasbourg at the end of October 2021. This time the new medical officer at work was against my return to work! However, I was able to produce a letter from Prof Caillard, certifying that the prophylactic medication I had received protected me, and I was authorized to resume work.

Receiving this antibody prophylaxis gave me my first sense of hope and relief as I could finally resume work despite the circulation of COVID-19 in the community. However, I was still feeling anxious. In fact, I was very well informed of the latest news about this treatment, and of the fact that there could be new variants of SARS-CoV-2 that are resistant to the monoclonal antibody therapy I had received. At work, I ate my lunch alone in my office and wore an FFP2 mask, while in my personal life, I maintained the same protective measures with my family and friends as during the lockdown. When the first Omicron variant arrived at the end of December 2021, I knew that the monoclonal antibodies I received may no longer be protecting me, and I again invoked the legislative decree concerning employees vulnerable to COVID-19 to work from home. This was until May 2022, when Prof Caillard told me that the health situation was safer for me because the second monoclonal antibody I received, tixagevimab-cilgavimab, had activity against the Omicron variant. Obviously, this new period of work from home has greatly disrupted my integration into my new position in Alsace.

The COVID-19 pandemic presented me with challenges I had never had to face before. It made me feel the need to get closer to an association for kidney disease patients, Renaloo (https://renaloo.com/). For the first time, it was nice to realize that I was not alone. For vulnerable patients like me, who had to be particularly vigilant during the pandemic, the public information circulating about COVID-19 was not sufficiently detailed or reliable. Following doctors' and scientists' accounts on Twitter provided more precise information; for example, it helped

me to understand the mode of transmission of the virus and to avoid unnecessary anxiety, especially when my husband contracted COVID-19. By taking simple measures such as wearing a mask during the day and having a separate room at night, I was able to avoid catching it.

With the pandemic, I went from having an invisible disability—my kidney transplant—which I could hide, to having a visible disability because I had to wear a mask all the time. It makes a big difference, first to you, but also to others. The current period, with its rapid succession of Omicron subvariants and the absence of effective prophylactic treatments, does not leave me at peace. Nevertheless, I am less and less anxious about the situation because I trust Prof Caillard. She has helped me understand that I am lucky as I have no other risk factors for severe COVID-19, and that the virus is evolving and may be becoming less harmful. Since April 2023, I have managed to relax my protection rules slightly, otherwise it would be unbearable. However, for me, the pandemic is not over.

NEPHROLOGIST'S PERSPECTIVE: PROF SOPHIE CAILLARD

I am Sophie Caillard, a nephrologist and head of the Department of Nephrology, Dialysis and Transplantation at Strasbourg University Hospital, France. I have been treating Elise since she moved to Alsace in 2021. In our center, we are currently monitoring a cohort of over 1700 kidney transplant recipients. Unless the donor is the patient's identical twin, any patient who receives a kidney transplant will need anti-rejection treatment to maintain kidney function for as long as possible. This immunosuppressive treatment must be taken every day, usually twice daily, for as long as patients have a transplant; the aim is to reduce their immune defenses and prevent them from rejecting the transplant. Today, the lifespan of a kidney transplant is around 13 years when it comes from a deceased donor and 20 years when it comes from a living donor [1]. Patients who develop kidney failure when they are young, like Elise, can therefore expect to receive several transplants during their lifetime and receive treatment with immunosuppressive drugs for many years. This raises the problem of the cumulative dose of these molecules and of the level of immunosuppression [2]. The lack of an immune response to COVID-19 vaccination can be linked to many factors, some of which are present in the general population, such as advanced age or diabetes. In solid organ transplant recipients, it is primarily related to immunosuppressive treatments [3, 4]. High dose of immunosuppressants, triple immunosuppressive regimens, and certain types of immunosuppressive agents (e.g., mycophenolate mofetil and belatacept), are associated with poor humoral response to SARS-CoV-2 vaccination [5–7]. Less than 10% of patients treated with belatacept (most of whom also received mycophenolic acid) show an antibody response to the vaccine, putting this population at high risk of infection with SARS-CoV-2 [8].

Given its geographical location and an early superspreader event, Strasbourg was confronted very early with numerous cases of COVID-19 and played a leading role in monitoring these patients and introducing procedures, particularly vaccination. We were very concerned about the health situation and wanted to protect our kidney transplant recipients as quickly as possible. Throughout the pandemic, we have gone through alternating phases of hope and disappointment. Indeed, 2020 was a very difficult year and, as doctors, we were very anxious for our patients. At the end of December 2020, we started vaccinating patients against SARS-CoV-2 with the messenger RNA (mRNA) vaccine, applying a protocol that enabled us to vaccinate patients as quickly as possible. Doctors and nurses came on weekends to vaccinate as many of our patients as we could.

About 1 month after the second dose of mRNA vaccine, we started performing serological testing and in March 2021, we reported that there were patients who did not show an effective humoral response to the SARS-CoV-2 vaccine after two injections [6]. Together with the French Transplantation and Nephrology societies (Société Francophone de Transplantation [SFT] and Société Francophone de Néphrologie, Dialyse et Transplantation [SFNDT]), we urgently went back to the authorities to obtain

authorization to vaccinate our kidney transplant recipients with a third dose. We obtained authorization in April 2021 and all patients were recalled to the hospital for administration of a third vaccine dose. Between April and August 2021, we realized that half of our cohort were still non-responders to the third dose of the SARS-CoV-2 vaccine, continued to be susceptible to infection with COVID-19, and remained at risk of developing a severe form of the disease [5]. For the other half, the antibody response improved.

In August 2021, the first prophylactic monoclonal antibody combination, casirivimab-imdevimab (Roche Regeneron) [9], was available in our hospital and we invited all patients who did not respond to the SARS-CoV-2 mRNA vaccine to receive this new COVID-19 preventive treatment. For 3 months—from September to November 2021—it was a great relief for us and for the patients. Some of them were able to return to work or an active social life. We were very pleased because we did not observe any cases of COVID-19 in our cohort even though the epidemic continued elsewhere.

Then, at the end of December 2021, the Omicron variant emerged along with several cases of COVID-19 in the cohort. This corresponds to the time when we had access to another prophylactic drug, tixagevimab-cilgavimab (AstraZeneca). We switched to this preventive treatment, which was promising as it was effective against the subvariant currently in circulation and had a long duration of action [10]. Patients who had not responded to the SARS-CoV-2 vaccine and who received tixagevimab-cilgavimab were informed that they were protected for approximately 6 months. However, we soon observed that the dose used—300 mg—was unable to induce sufficiently protective levels of neutralizing antibodies against some Omicron subvariants in a subset of patients. After further discussions with the health authorities regarding authorization to administer a higher dose of tixagevimab-cilgavimab, approval to double the dose was obtained at the end of April 2022. As one of the first hospitals in France to administer this prophylactic drug, we had to contact all patients again to administer a second dose of tixagevimab-cilgavimab, while some other centers were able to administer the 600 mg dose at the time of the first injection. Ultimately, most patients in our cohort were administered the appropriate dose of tixagevimab-cilgavimab. In spring 2022, the Omicron subvariants emerged, and the situation once again became difficult and uncertain for us and our patients, with a succession of subvariants that were more or less sensitive to tixagevimab-cilgavimab [11, 12]. From both the patients' and the physicians' perspectives—and indeed that of the health authorities—the COVID-19 pandemic has required continuous adaptation.

The case of Elise illustrates the situation of many immunocompromised patients who cannot be protected efficiently by the SARS-CoV-2 mRNA vaccine. She is being treated with an immunosuppressive regimen—belatacept and mycophenolate mofetil—that induces a low protective antibody response, and she has not responded to the vaccine despite receiving all the necessary doses. We discussed with Elise the possibility of changing her immunosuppressive treatment, but we agreed that we did not want to take the risk of exposing her graft to a molecule that might be more toxic or exposing her to the risk of transplant rejection. When immunosuppressive treatment is changed, in most cases, the risk to the patient of transplant damage is greater than the risk of SARS-CoV-2 infection itself, even though it remains a severe infection. In Alsace, as we were heavily impacted by the COVID-19 epidemic, the supply of vaccine or prophylactic monoclonal antibodies was optimal, which was not always the case in other French centers. Elise was able to receive the two monoclonal antibody combinations available on the market for prophylaxis, casirivimab-imdevimab and tixagevimab-cilgavimab.

In the current Omicron era with its multiple subvariants, some of our patients responded well to the vaccine and continued to receive booster doses; others showed poor immune response against SARS-CoV-2 and were no longer protected against COVID-19 because of a lack of effective prophylactic monoclonal antibodies. Among the non-responders, there were two scenarios: some patients did not want to receive booster injections because they knew they were not responding to the vaccine, while others

continued to receive them in the hope that their immunity would eventually be stimulated, which is likely [13]. Currently, no prophylactic monoclonal antibody is fully effective in protecting immunocompromised patients against rapidly evolving Omicron subvariants, but this is continuously evolving. On the other hand, two antiviral drugs—nirmatrelvir-ritonavir and remdesivir—given in a curative manner are effective in preventing progression to a severe form of COVID-19 in infected transplant recipients [14, 15]. A major concern with using nirmatrelvir-ritonavir is its potential for interaction with immunosuppressive drugs, requiring doses to be adapted and complicating immunosuppression management in solid organ transplant recipients [16]. Today, the situation is much more manageable because COVID-19 is better controlled in terms of severity and management than it was in 2020 or 2021. In 2020, the 1-month mortality associated with COVID-19 in at-risk kidney transplant recipients was around 20% [17], while the mortality currently attributed to Omicron is around 2% in solid organ transplant recipients [18]. Our hope is that, in collaboration with pharmaceutical companies, we will be able to find in vitro tests capable of predicting the efficacy of prophylactic monoclonal antibodies against circulating variants of concern in our patients, and that the authorities will validate the use of new effective antibodies without having to resort to large-scale, time-consuming clinical trials, in a scenario where in vitro neutralizing tests show conclusive results.

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Declarations

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