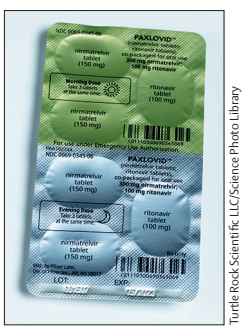
Refining COVID-19 care for immunocompromised patients



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Since 2022, with the emergence of highly transmissible omicron variants and the relaxation of social distancing measures, protecting individuals who are immunocompromised from SARS-CoV-2 exposure has become increasingly difficult. As a result, these patients have been more frequently reported to have severe and persistent COVID-19.[1,2] Currently, most COVID-19-related consultations performed by infectious diseases' doctors concern managing COVID-19 in patients who are immunocompromised.

Patients unable to mount an effective humoral response against SARS-CoV-2 are at particularly high risk. These individuals include people with hypogammaglobulinemia or agammaglobulinemia, individuals receiving B-cell depleting therapies or chimeric antigen receptor (CAR) T-cell therapy, and solid-organ and haematopoietic stem-cell transplantation recipients. Unfortunately, little data exist to guide treatment in these patients, and current clinical guidelines often recommend a uniform approach.[3] Key unanswered questions include how to treat severely immunocompromised patients with acute, non-complicated COVID-19 to prevent severe or persistent COVID-19; what the optimal treatment is for persistent COVID-19; and when immunosuppression can be safely resumed in these patients.

In *The Lancet Infectious Diseases*, Edward Weinstein and colleagues provide valuable data addressing the first question.[4] In this Pfizer-sponsored, multicentre, placebo-controlled trial, immunocompromised patients with COVID-19 were randomly assigned to receive nirmatrelvir–ritonavir for 5, 10, or 15 days within 5 days of diagnosis. Participants were monitored frequently until day 44, with additional follow-up at 3 and 6 months. The primary outcome was sustained viral suppression from day 15 to day 44. At first glance, the results suggest that treatment duration had no effect, as 30–40% of patients did not maintain undetectable SARS-CoV-2 after treatment, regardless of its duration. However, a post-hoc analysis suggested potential benefits of extended treatment for severely immunocompromised patients, including those with haematological malignancies, B-cell depleting therapies or CAR-T-cell therapy recipients, and patients with haematopoietic stem-cell transplantation. Sustained viral suppression occurred more frequently in severely immunocompromised patients treated for 10 days (64·7%) compared with those receiving 5 days of treatment (35%), but not in patients treated for 15 days (40%), although differences versus the 5-day treatment group were not significant, even when the two longer treatment groups were combined. Additionally, for the entire cohort, longer treatment was associated with a non-significant decrease in time to sustained suppression (10 days or 11 days *vs* 15 days). Participants who were PCR-positive were also frequently symptomatic, and longer treatment duration was associated with a shorter time to becoming symptom free for the entire cohort. This finding might have important implications for patients who stop immunosuppression until clinically and virologically cured.[5]

Post-treatment viral rebound, a well documented phenomenon in clinical practice and literature, was more common in the 5-day group and occurred in 17% of the overall cohort and 25% of the severely immunocompromised subgroup who received treatment for 5 days, compared with 0–5% of participants in the longer treatment groups. Although viral rebound after treatment occurred at similar rates in both nirmatrelvir-treated and placebo-treated patients in the EPIC randomised studies, observational studies[6] with an increased frequency of testing reported that nirmatrelvir-treated patients were more likely than untreated patients to test positive for SARS-CoV-2 within 15 days (27% *vs* 7%). Although the clinical implications of viral rebound remain unclear in the general population, in severely immunocompromised individuals viral rebound might signal the onset of persistent COVID-19, particularly when accompanied by symptom recurrence. Weinstein and colleagues report only one late virological relapse, in the 10-day treatment group. However, since participants were tested only twice over 6 months, additional cases of relapse might have been undetected. The only two COVID-19-related hospitalisations in the study occurred in severely immunocompromised patients who received the 5-day regimen.

Longer treatment durations were associated with a slightly higher number of adverse events, primarily mild and transient (eg, dysgeusia), and no cases of nirmatrelvir-resistant viral mutations were detected. This result is reassuring, although previous

reports have documented resistance emerging in immunocompromised patients receiving prolonged antiviral therapy with remdesivir[7] and nirmatrelvir.[8]

Weinstein and colleagues should be commended for their effort to provide evidence-based guidance on COVID-19 management for immunocompromised patients. However, the study population might not have been ideal; many of the participants were not severely immunocompromised and so seemingly less likely to benefit from prolonged treatment. The sample of severely immunocompromised patients was too small to provide conclusive results. Thus, the question on how severely immunocompromised patients with acute, non-complicated COVID-19 should be treated to prevent severe or persistent COVID-19 remains only partially answered. The results of the study add to existing observational data, suggesting that some immunocompromised patients might require extended treatment beyond the standard regimen. Prolonged treatment appears to enhance virological response, reduce viral rebound, and potentially improve clinical outcomes. Additional therapeutic strategies, including antiviral combination or incorporation of antibody-based treatments, such as monoclonal antibodies or convalescent plasma, have been proposed.[2]

As COVID-19 continues to pose a substantial health threat to severely immunocompromised individuals, further research is urgently needed to refine treatment strategies and improve outcomes for this vulnerable population.

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