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Research note

Viral dynamics of SARS-CoV-2 in immunocompromised patients

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ABSTRACT

Objectives: Immunocompromised patients infected with SARS-CoV-2 have been shown to shed replicable virus for a prolonged period of time, and the duration of isolation can therefore be difficult to estimate. The objective of this study was to evaluate the viral load dynamic in non-hospitalized immunocompromised patients infected with SARS-CoV-2 and treated with monoclonal antibodies (mAbs) or antivirals.

Methods: Oropharyngeal swabs for RT-PCR and viral culture were collected from 29 immunocompromised patients before treatment with mAbs or antivirals and at days 5 and 15 after treatment. Overall, 12 patients were infected with the subvariant Omicron BA.1, 12 with Omicron BA.2, two with the Delta variant and for three patients determination of the variant were inconclusive.

Results: Before treatment with mAbs or antivirals, 22 of 29 patients (76% [95% CI, 56–90]) shed replicative SARS-CoV-2. At day 5, 21 patients (72% [95% CI, 53–87]) still tested RT-PCR–positive, but for 14 patients (48% [95% CI, 29–67]) there were no replicative virus in culture. At day 15, 16 patients (55% [95% CI, 36–74%]) tested positive but only two patients (7% [95%CI, 1–23]) had replicative virus.

Discussion: Half of the patients in this cohort had no viable virus after 5 days and only two patients had replicative virus after 15 days. This could indicate that the current CDC recommendations of an isolation period of 20 days for immunocompromised patients infected with SARS-CoV-2 could be reduced, but larger studies are needed to estimate the isolation duration for immunocompromised patients. **Andrea N. Utzon, Clin Microbiol Infect 2023;29:1087.e1–1087.e3**

Introduction

Immunocompromised patients infected with SARS-CoV-2 have a longer duration of infectiousness and cases have shown shedding of viable virus for a prolonged period of time up to 70 days [1,2]. Therefore, it provides a common dilemma for clinicians to decide the duration of isolation in these patients. Current guidelines from the CDC suggest an isolation period of at least 20 days after a positive test for moderately to severely immunocompromised patients and a test-based strategy thereafter [3].

The strategy for treating non-hospitalized immunocompromised patients infected with SARS-CoV-2 has since autumn 2021 and until recently been early treatment with antivirals and/or neutralizing monoclonal antibodies (mAbs), depending on the degree of immunosuppression [4,5]. Monoclonal antibodies have shown reduced risk of disease progression and hospitalization in high-risk patients [6,7]. However, the effect amongst immunocompromised patients has only been evaluated in case studies [8,9]. In an outpatient setting, treatment with Remdesivir yielded an 87% decrease in the risk of disease progression, though only 4.1% of the patients were immunocompromised [10]. The impact of the drug on viral shedding and the duration of its infectiveness have not been clearly estimated, though a randomized study by Wang et al. [11] did not show a difference in viral load decline between non-immunocompromised patients treated with Remdesivir or placebo.

The objective of this study was to evaluate the viral load dynamic of SARS-CoV-2 measured by RT-PCR and virus isolation from

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non-hospitalized immunocompromised patients infected with SARS-CoV-2 treated with antivirals or mAbs.

Method

Patients were included between 17 December 2021 and 28 February 2022 at the Department of Infectious Diseases, Odense University Hospital, Denmark. Adult high-risk non-hospitalized immunocompromised patients received treatment for a maximum period of 6 days after their first positive RT-PCR-test for SARS-CoV-2. High-risk patients were defined as patients with 1) haematological malignancies, 2) solid organ transplantation or 3) treatment with CD20-antibodies within <6 months in non-haematological patients. All participants signed informed consent and participants could withdraw their consent at any time. This study was approved by the Regional Committees on Health Research Ethics for Southern Denmark (ID S-20200047C) and the Danish Data Protection Agency (j. no 20/16202). Oropharyngeal swabs for RT-PCR and culture were collected before treatment and at day 5 and 15 hereafter. Detailed specifications on the RT-PCR and the viral culture used in the study have previously been described [12] and can be reviewed in short (please see supplemental material). For statistical analyses we used Students t-test to evaluate the difference in mean Ct-values and Fisher's exact test to evaluate if there were difference in replicability, when patients were stratified according to treatment and virus subtype, respectively.

Results

In total, 31 patients were included in the study. Two patients were excluded in the analyses, one with negative PCR before treatment and one patient lost-to-follow-up after treatment. Patient characteristics are shown in Table 1.

The results from the RT-PCR and the viral culture are shown in Fig. 1. Before treatment, 22 patients were shedding replicative SARS-CoV-2 and their mean Ct-value were 23.0 (range, 18.3–33.1), compared to a mean value of 31.5 (range, 21.9–37.9) for the patients with non-replicative virus in their samples. None of the patients with non-replicative virus at day 0 had viable virus during the study period. On day 5, four patients had negative PCR-tests, 21 had positive PCR-test whereas four patients did not provide a swab sample. A total of 67% (14/21) (95% CI, 43–85) of those with positive PCR-tests did not have any replicative virus in culture. The mean Ct-value at day 5 was 32.6 (range, 26.1–36.7) for the culture-negative and 27.9 (range, 23.9–29.7) for the culture-positive samples. Furthermore, at day 15, 13 patients had negative PCR-tests whereas 16 patients had positive PCR-tests of which only two patients had viable virus. The two patients were both solid organ transplant recipients, infected with Omicron BA.1 and one was treated with Sotrovimab and the other with Remdesivir. When comparing the results according to the different variants or treatment, we did not find significant differences between them.

Table 1
Patient characteristics

Study population, *n*	29
Women, *n* (%)	13 (44.8 %)
Men, *n* (%)	16 (55.2%)
Age (y), median (IQR)	53 (42–58)
High-risk condition	
Haematological malignancy, *n* (%)	8 (27.6%)
Solid organ transplant, *n* (%)	11 (37.9%)
Treatment with CD-20-antibodies within 6 months prior to inclusion, *n* (%)	10 (34.5%)
Vasculitis, *n* (%)	6 (20.7%)
Multiple sclerosis, *n* (%)	4 (13.8%)
Number of COVID vaccine doses per patient	
2, *n* (%)	1 (3.4%)
3, *n* (%)	26 (89.7%)
4, *n* (%)	2 (6.9%)
Variant subtype	
Omicron BA.1, *n* (%)	12 (41.4%)
Omicron BA.2, *n* (%)	12 (41.4%)
Delta, *n* (%)	2 (6.9%)
Inconclusive, *n* (%)	3 (10.3%)
Treatment	
Sotrovimab, *n* (%)	25 (86.2%)
Regen-Cov, *n* (%)	1 (3.4%)
Remdesivir, *n* (%)	16 (55.2%)
Both mAbs and Remdesivir, *n* (%)	13 (44.8%)

IQR, interquartile range; mAbs, monoclonal antibodies.

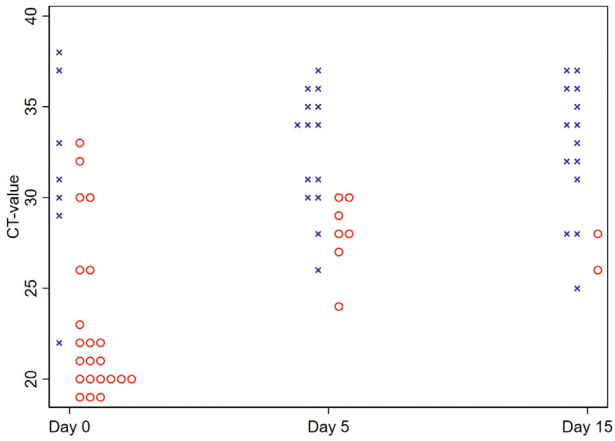

Fig. 1.

Discussion

Our data shows that replicative virus could not be retrieved 15 days after initiating treatment with mAbs and/or antivirals for 93% (95%CI, 77–99%) of the included immunocompromised patients. Furthermore, 55% (95%CI, 36–74%) still tested RT-PCR-positive at day 15 but only two patients presented with replicative virus. All patients had increasing Ct-values during the study course except the two patients with replicative virus at day 15.

A systematic review from 2021 by Cevik et al. [13], not focusing on immunocompromised patients and conducted before the Omicron variant emerged, found that although viral shedding could persist for up to 83 days, there were no evidence of replicative virus after day 9 of symptom onset. In a recent study by Kang et al. [14] patients infected with the Omicron variant had a shorter period of viral shedding than patients with the Delta variant, with a median of 4 and 8.5 days respectively, and the Omicron variant was found to be associated with shorter viability also when adjusting for immunocompromised conditions. Current isolation guidelines is based on previous SARS-CoV-2 variants where the risk of disease progression were higher [3]. Furthermore, it is also reasonable to speculate that the extensive roll-out of the COVID-19 vaccines and the continuously development of early treatment with mAbs and antivirals to immunocompromised patients has an impact of viral shedding.

As isolation is draining for both patient quality of life and hospital resources, it is desirable to shorten this period as much as safely possible. In our study, we found that half of the patients had no viable virus in high-sensitive flask cultures after only 5 days and this could indicate that the isolation period for some of these patients could be markedly reduced. However, two patients infected with BA.1 still had replicative virus after day 15. This also illustrates that with current treatment regimens and SARS-CoV-2 variants,

there are still patients who shed replicative virus for prolonged periods of time, which demonstrates the need for larger studies in relation to individualize the length of isolation for immunocompromised patients. Further studies have to clarify if it could be possible to develop an algorithm with simple parameters to estimate the time of isolation. Our data shows that patient samples with Ct-values >30 after 5 days were all non-replicative in culture. This indicates that patients with samples above this value can probably be safely removed from isolation.

A limitation to this study is that both Ct-values and the viral cultures are dependent on the quality of the oropharyngeal swabs [15]. An effort was made by trained personnel to retrieve adequate and equal sample material, but there may still be variation. All our samples were frozen and thawed twice but data from our own lab indicate that the impact on viability is small when samples are in the right preservation media and are not stored at room temperature (unpublished data). Furthermore, our cohort was not large enough to examine if there are certain risk factors that increase the probability of prolonged presence of replicable virus. Finally, the results cannot be extrapolated to all immunocompromised patients, as every type of immunosuppression could affect the viability of the virus differently.

Whether our findings are related to individualized characteristics or treatment with mAb or antiviral treatment is unknown. However, this study provides a real-life perspective on the dynamics of the virus in a heterogenic group of immunocompromised patients treated according to national guidelines at the time but larger studies are needed to determine whether isolation can be shortened for immunocompromised patients.

Author contributions

IJ conceptualized the study. LB, RP and TA performed the laboratory analysis. LM and LB performed the investigation. AU performed the data analysis and wrote the original draft with supervision from LM. All authors contributed equally to methodology, review and editing.

Transparency declaration

The authors declare that they have no conflicts of interest. The study received no external funding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.05.013.

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