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Concise Communication

Duration of isolation and contagiousness in coronavirus disease 2019 (COVID-19) patients receiving tocilizumab and dexamethasone: A case series

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Abstract

We describe 10 patients with severe coronavirus disease 2019 (COVID-19) who received tocilizumab and dexamethasone. We correlated isolation duration with cycle thresholds (Ct) values of nucleic acid amplification tests, clinical state and viral cultures. Isolation duration exceeded 21 days for 7 patients due to positive viral cultures or Ct values <30.

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Coronavirus disease 2019 (COVID-19) contagiousness is critical in the healthcare setting, and it varies along with severity of disease, immunosuppression of host, and medication.[1] In severe cases of COVID-19, viral replication and transmission have been described up to 20 days after the onset of symptoms, sometimes longer in immunocompromised patients.[2,3] Still, the Centers for Disease Control and Prevention (CDC) guidelines recommend removal from isolation 21 days after the onset of symptoms, after resolution of fever and improvement of symptoms. A test-based strategy "can be considered."[4]

In the province of Quebec, Canada, a single dose of tocilizumab along with 10 days of dexamethasone are recommended in severe cases of COVID-19. Considering the relative immunosuppression induced by those drugs[5,6] and the fact that they are used in severe cases, uncertainty regarding the optimal duration of isolation surfaced. One study showed that tocilizumab and dexamethasone treatments were independently associated with prolonged shedding of viral RNA.[1]

We can assess contagiousness and viral replication through viral culture.[7] Unfortunately, this method takes time and specialized laboratories. Alternatively, we can evaluate viral shedding and extrapolate contagiousness through cycle threshold (Ct) values of nucleic acid amplification tests (NAATs) of SARS-CoV-2 RNA.[7]

We describe 10 patients who received tocilizumab and dexamethasone for severe COVID-19 due to the α (alpha) variant (B.1.1.7). We correlated clinical state, Ct values of NAAT, and viral culture results to suggest safe discontinuation of isolation measures.

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Methods

Patient selection

We reviewed cases of severe COVID-19 that occurred in our institution from March 23 through April 21, 2021. We included every patient who received tocilizumab and dexamethasone for whom isolation duration was evaluated by an infectious disease (ID) consultant. We reviewed comorbidities, symptomatology and temperature, isolation duration, and NAAT results, and viral culture results.

Setting

The Centre Hospitalier Universitaire de Québec-Université Laval is a 1,660-bed, acute-care university institution in Quebec City, Canada. The COVID-19 patients are hospitalized on COVID-19–specific units with dedicated staff for their isolation duration, then they are transferred to non–COVID-19 wards. The COVID-19 units comprise ~115 beds and 15 ICU beds in 2 separate sites.

Diagnostic tests

The decision to obtain NAAT or viral culture was delegated to the ID consultant. All specimens were obtained through nasopharyngeal swabs. NAAT were conducted on Simplexa assay (DiaSorin Molecular), targeting genes S and ORF1ab. Viral cultures were done on Vero E6 cells in a Biosafety level 3 laboratory, using a previously described method.[8] After a year-long pause (as a biosafety mitigation measure), viral cultures were allowed again in our institution in March 2021, if prescribed by an ID specialist to evaluate patients post tocilizumab and dexamethasone. Our case series includes every viral culture performed within the study period.

Table 1. Patient Characteristics, Comorbidities, Date of Onset of Symptoms, Intubation, Results of NAAT and Viral Cultures and Isolation Duration

Patient	Sex and Age	Comorbidities	Date of Onset of Symptoms	Intubation Duration, Days	Evolution at Day 21 After OOS	NAAT Results, Day (Ct gene S/gene ORF1ab)	Viral Culture Result (Day of Sample From OOS)	Reason to Lift Isolation	Lifting Isolation After OOS Day
1	M, 66	Idiopathic pulmonary fibrosis (mild), HTN, Type 2 diabetes, DYSLIPIDEMIA	March 23, 2021	28 (until death 29/04)	Clinical deterioration, hypoxemia, ongoing fever under large spectrum antibiotics	Positive day 21 (21.2/21.9) Positive day 30 (28.2/28.5) Positive day 31 (19.3/19.4) Positive day 33 (22.2/21.5)	Positive in 3 days (day 33)	Not lifted, Deceased on day 37	Not lifted
2	F, 60	Depression, migraine, obesity	April 15, 2021	12	Clinical improvement, subfebrile on UTI	Mild positive day 21 (31.3/ND) Mild positive day 25 (ND/34.3)	Negative (day 21)	Negative culture	28
3	M, 60	HTN, type 2 diabetes, dyslipidemia	April 4, 2021	39	Persistent hyperthermia, hypoxemia still under mechanical ventilation, bacteremia	Positive day 36 (24.3/25.2) Positive day 38 (29.9/30.7) Positive day 40 (16.4/17.7) Positive day 43 (19.9/20.9) Positive day 45 (28.8/29.2)	Negative (day 37)	Negative culture	45
4	M, 57	HTN, type 2 diabetes, dyslipidemia	April 21, 2021	9	Afebrile, clinical improvement	Positive day 21 (23.4/24.4) Positive day 23 (31.4/33.8)	Positive in 2 days (day 21)	Clinical improvement and Ct > 30	23
5	M, 59	HTN, previous aortic dissection, chronic renal insufficiency (stage 2), bronchial hyperreactivity (mild), previous upper gastrointestinal bleeding	April 5, 2021	38 (tracheostomy at day 22)	Intermittent hyperthermia, still under mechanical ventilation, broad- spectrum antibiotics to cover ventilator-acquired pneumonia	Negative day 37 Negative day 39	Negative (day 37)	2 negative nasopharyngeal NAATs	39
6	M, 75	HTN, obstructive sleep apnea, coronary artery disease, osteoporosis, hypothyroidism	April 21, 2021	5	Afebrile, clinical improvement	No NAAT done after diagnosis	Negative (day 21)	Clinical criteria	21
7	M, 51	Obstructive sleep apnea, esophageal reflux, previous nasal septal deviation surgery	April 2, 2021	10	Afebrile, clinical improvement	Positive day 24 (31.2/32.7)	Negative (day 24)	Clinical criteria. Isolation extended because date of onset of symptom initially not clear – was thought to be on Day 21 post OOS.	24
8	M, 66	HTN, hepatitis B undergoing treatment (Entecavir), possible lymphoma under investigation	April 13, 2021	10	Afebrile, clinical improvement	Negative day 28	Not done	Clinical criteria. Isolation extended because date of OOS was initially not clear and was thought to be on day 21 after OOS.	28
9	M, 46	Obesity, callous body agenesia	April 17, 2021	16	Still febrile, clinical amelioration	Positive day 23 (27.1/28.2) Negative day 32	Note done	Negative NAAT	33
10	M, 70	HTN, obstructive sleep apnea, esophageal reflux, dyslipidemia, coronary artery disease, migraine, previous prostate neoplasia	April 7, 2021	13	Afebrile, clinical improvement	Positive day 21 (20/20.8) Positive day 28 (30/30.2) Positive day 29 (32.8/35.4)	Negative (day 21)	Clinical improvement and Ct >30	29

Note. NAAT, nucleic acid amplification test; M, male; F, female; HTN, arterial hypertension; UTI, urinary tract infection; OOS, onset of symptoms; ND, not detected.

Infection control

According to local guidelines, patients presenting with severe illness (defined as intensive care warranting high-flow oxygen or mechanical ventilation) could be removed from isolation after 21 days if they had been apyretic for 48 hours and clinically improving for 24 hours. Isolation duration could be extended by ID specialists, when called upon. As a clinical surrogate for our patients' contagiousness, we monitored new COVID-19 cases in healthcare workers and other patients on non–COVID-19 wards after removal from isolation.

Results

Patients aged 46–75 years who had a severe case of COVID-19 (α variant) and received a single dose of tocilizumab along with dexamethasone for 10 days were included in this study. They all needed invasive ventilation for a period ranging from 5 days to >1 month. They did not receive any other COVID-19–specific treatment. Every patient but one recovered.

Overall, there is a discrepancy between our results (Table 1) and approved guidelines concerning duration of isolation for severe COVID-19. At day 21 after onset of symptoms, 7 of 10 patients remained in isolation, mostly because of lack of clinical improvement, low Ct values, and, in 2 cases, positive viral cultures.

No secondary COVID-19 infection on non–COVID-19 wards were identified when isolation measures were lifted.

Discussion

Our case series advocates against the deisolation of severely ill COVID-19 patients who receive tocilizumab and dexamethasone based on clinical improvement alone at day 21. Of 10 patients, 5 had Ct values <30, and 2 patients had a positive viral culture after day 20, which contrasts with previous data.[4,7] The use of tocilizumab and dexamethasone in our case series may have contributed to a prolonged viral shedding, along with severe infection. More research is needed to determine the underlying causes and risk factors of prolonged infectivity.

Our research reflects what is currently known on the correlation between high NAAT Ct values and negative culture, past a certain threshold. Ct values may vary with the technology used—5 studies reported no growth on viral culture on specimen with Ct values ranging from > 24 to >35.[7] Because the Simplexa assay does not require molecular extraction, Ct values can be somewhat lower than with other methods (−2.1 cycles compared to the CDC diagnostic panel).[9]

Ct values fluctuated substantially over multiple days samplings, which might represent variable shedding linked to specimen quality or volume and severity of disease.[3] Patients with prolonged positive testing (>28 days) have also been shown to be the ones in whom Ct values fluctuate the most,[3] which was the case for patient 3, notably.

For severe COVID-19 cases after tocilizumab and dexamethasone, our data advocates for a deisolation strategy based on 2 separate NAAT results (thus mitigating the fluctuation of Ct values); a conservative Ct cutoff value >30 could be used in clinically improving patients at least 21 days after symptoms onset. In our case series, Ct values >30 in clinically improving patients correlated with negative viral culture (and presumed absence of contagiousness[7]). After lifting isolation, no secondary infection was attributed to our patients. It is possible (but unlikely) that they were still contagious but did not infect others due to infection prevention and control measures. Conversely, the fact that some patients have a prolonged viral excretion might explain some of the nosocomial outbreaks seen during the pandemic.

The principal strength of this case series is that we have presented viral culture results, whereas while most previous studies have shown RNA viral shedding through NAAT alone. Providing detailed case summaries might also be of use to clinicians. Finally, to our knowledge, few other studies have addressed the impact of tocilizumab and dexamethasone on isolation duration.

The principal limitation of our case series was its small sample size, which precludes strong conclusions and generalization. Nonetheless, our patients' age and comorbidities reflect COVID-19 ICU population. All patients presented with the α (alpha) variant, the most prevalent variant at the time in our province. Notably, due to clinicians' autonomy and laboratory workers' unavailability on weekends, cultures could not be systematically obtained at day 21. Reflecting real-life situations, our case series was conducted without a control group.

Relying on NAAT results in addition to clinical criteria is the safest option in our opinion, considering positive viral culture obtained in a clinically improved patient. Additionally, using NAAT as an objective surrogate for contagiousness probably constitutes the best option in view of newer variables: vaccination status, breakthrough infections, and variants of concern, especially o (omicron) and δ (delta) variants. The δ variant has been associated with longer duration of Ct values <30.[10] Larger trials are needed to confirm our data and to explore its applicability in those situations.

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