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COVID-19 infection and blood monitoring via ZTAS

Many healthcare professionals may have questions concerning the effect of the current corona virus pandemic on the use of Zaponex® (clozapine), and especially the mandatory blood tests. We have checked some health authority sites, and the CDC, WHO and MHRA provide some helpful advice to HCPs. Please note that the following is only meant as a guideline rather than a definite treatment strategy, as all treatment choices are ultimately clinical decisions:

Disease transmission and course

COVID-19 is the official WHO designation of the disease caused by the SARS-CoV-2 virus, although some organisations may still use the term COVID-19 to indicate the virus. The mode of transmission is thought to occur via cough and sneeze droplets, which are then inhaled by others, or picked up by their hands and transferred when touching their face. There is currently no evidence to suggest that the virus can be transmitted from food, via pets, or through post, packages or parcels from infected areas.

The incubation of the disease period is estimated at ~5 days (95% confidence interval, 4 to 7 days), but may range from 2-14 days. Frequently reported signs and symptoms include fever (83–98%), dry cough (46%–82%), myalgia or fatigue (11–44%), and shortness of breath (31%) at illness onset. Sore throat has also been reported in some patients early in the clinical course. Less commonly reported symptoms include sputum production, headache, haemoptysis, and diarrhoea. Gastrointestinal symptoms such as diarrhoea and nausea may precede the fever and lower respiratory tract signs and symptoms. The fever course may be prolonged and intermittent.

Older patients and those with chronic medical conditions may be at higher risk for severe illness. Approximately one-third to one-half of reported patients had underlying medical comorbidities, including diabetes, hypertension, and cardiovascular disease. In another study, compared to patients not admitted to an intensive care unit, critically ill patients were older (median age 66 years versus 51 years), and were more likely to have underlying co-morbid conditions (72% versus 37%).

Clinical presentation among reported cases of COVID-19 varies in severity from asymptomatic infection or mild illness to severe or fatal illness. Some reports suggest the potential for clinical deterioration during the second week of illness. Acute respiratory distress syndrome (ARDS) developed in 17–29% of hospitalized patients, and secondary infection developed in 10%. Between 23–32% of hospitalized patients with COVID-19 and pneumonia have required intensive care for respiratory support. Some hospitalized patients have required advanced organ support with endotracheal intubation and mechanical ventilation (4–10%), and a small proportion have also been supported with extracorporeal membrane oxygenation (ECMO, 3–5%). Other reported complications include acute cardiac injury, arrhythmia, shock, and acute kidney injury. Among hospitalized patients with pneumonia, the case fatality proportion has been reported as 4–15%. However, as this estimate includes only hospitalized patients it is biased upward. Nosocomial transmission among healthcare personnel and patients has been reported.

Using available preliminary data, the median time from onset to clinical recovery for mild cases is approximately 2 weeks and is 3-6 weeks for patients with severe or critical disease. Preliminary data suggests that the time period from onset to the development of severe disease, including hypoxia, is 1 week. Among patients who have died, the time from symptom onset to outcome ranges from 2-8 weeks.

In case of suspicion of infection, use the NHS 111 online coronavirus service to find out what to do (https://111.nhs.uk/covid-19).

There are currently no antiviral drugs licensed by the U.S. Food and Drug Administration (FDA) nor European Medicines Agency (EMA) to treat patients with COVID-19. Some in-vitro or in-vivo studies suggest potential therapeutic activity of compounds against related coronaviruses, but there are no available data from observational studies or randomized controlled trials in humans to support recommending any investigational therapeutics for patients with confirmed or suspected COVID-19 at this time. Remdesivir, an investigational antiviral drug, was reported to have in-vitro activity against SARS-CoV-2. A small number of patients with COVID-19 have received intravenous remdesivir for compassionate use outside of a clinical trial setting.

Sources: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html; https://publichealthmatters.blog.gov.uk/2020/01/23/wuhan-novel-coronavirus-what-you-need-to-know/; https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

Clozapine use and COVID-19

There is currently no data that suggests that clozapine patients should not continue to take their clozapine if they are suspected to have contracted COVID-19. Although specific information is lacking, we refer to our standard information with regards to clozapine use in patients with influenza or other airway infections.

As per the Summary of Product Characteristics of clozapine: “At each consultation, a patient receiving clozapine should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia. Patients and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately.”

In case of a confirmed concurrent flu or infection, our advice would be to actually increase the FBC frequency rather than decrease, as such infections can cause quick drops in both WBCs and neutrophil counts (NCs). It is recommended to continue doing frequent blood tests as long as the patient shows symptoms of the flu/infection. Weekly bloods may be appropriate, but this is a clinical decision that may have to be discussed by a haematologist.

Please note that bacterial or viral infections have been reported to increase clozapine plasma levels. In patients who develop clozapine overdose symptoms such as drowsiness, sedation, lethargy, confusion, agitation, tachycardia, hypotension, respiratory depression and seizures, high plasma levels should be suspected and a plasma level assay should be done to confirm or exclude this. In positive cases, the clozapine dose may need to be temporarily reduced until the infection resolves. Since the results of these assays can take some days to come in, it may be necessary to do an anticipatory dose reduction in patients who display symptoms of both infection and overdose. Please see our fact sheet ‘Clozapine metabolism and plasma level monitoring’ for more information (available via the information button on the ZTAS website).

Preventive measures

It is well-known that centralised monitoring of leukocyte and neutrophil counts is a mandatory requirement for all patients in the UK who are treated with Zaponex, which can be a challenge when there is a significant risk of COVID-19 infection. The CDC and MHRA have full safety protocols for dealing with suspected COVID-19 patients when testing for the CoV-2 virus (including the use of airborne infection isolation rooms, respirators and eye protection; see https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html).

Although these would also seem to apply for ZTAS patients suspected or already diagnosed with COVID-19, such measures are probably too elaborate, costly and impractical for most local clinics and communities that need to collect blood for clozapine monitoring. With some common sense and simple precautions, the risk of infection can probably be minimised. Some practical tips include:

- keeping patients separately from non-infected people, preferably at home; if patients cannot be kept completely separate for longer times, maintain appropriate distance (at least 6 ft).

- observing respiratory and hand hygiene, as well as cough etiquette. This includes: washing/sanitising hands often; avoid touching eyes, nose and mouth with unwashed hands; using disposable tissues and cough/sneeze into one's elbow, sleeve or a tissue instead of hands (dispose of tissue immediately afterwards).

- outfitting patients with a facemask if possible (masks need to cover both nose and mouth, and have to be handled and disposed of correctly).

- HCPs should use alcohol-based hand sanitiser before and after all contact with patients and potentially infectious material, and before putting on and upon removal of personal protective equipment (PPE), including gloves.

With regards to the first point, we suggest that the site should try to avoid having suspected COVID-19 patients come to the clinic, and consider the possibility of testing them at home. This would involve taking into account the appropriate measures for self-protection of HCPs (gloves, protective glasses, face mask, frequent handwashing and respiratory hygiene) and subsequently testing of the blood sample on the PoCHi machine, as patients with signs of a possible agranulocytosis (such as sore throat, fever) should be tested more frequently. A community nurse or the patient's GP could possibly execute or arrange the blood sampling.

There is no waiver for blood monitoring, and we are aware that it may be increasingly difficult to get blood from patients due to home isolation or risk of spreading an infection. It is thus suggested to use the extended validity in blood tests to limit the number of tests: patient on weekly bloods have a maximum test validity (and Zaponex supply) of 14 days; for fortnightly patients it is 21 days, and for monthly patients 42 days (although we advise against waiting until the final day of blood validity). Current observations suggest that mild cases of COVID-19 seem to last a few weeks at most, so this when clinically acceptable is an in-license option that allows clinicians some manoeuvrability around testing.

The decision to deviate from the regulatory recommendations for clozapine monitoring would be at the treating physician's discretion based on a benefit-risk assessment. However, as this would constitute unlicensed use of our product, please inform us if Zaponex will be used under off license conditions.

Analysis of blood samples

In the event that blood samples can no longer be sent to our central laboratory Magna Laboratories (in case Royal Mail and/or couriers do no longer function properly), please analyse samples locally. Subsequently enter the results onto ZTAS (ZTAS registration required), forward the results to ZTAS per email at info@ztas.co.uk or alternatively fax results to ZTAS using fax number 0207 365 5843.

Support by ZTAS

Leyden Delta and ZTAS will work with the relevant Health Trusts and Health Boards to manage your patients. We have a 24/7 availability via (telephone) 0207 365 5842.

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