

Timely Treatment, Rapid Recovery: Addressing the Burden of Acute COVID-19 in High-Risk Patients

Introduction

Dr Michele Bartoletti: Welcome to this educational program called Timely Treatment, Rapid Recovery: Addressing the Burden of Acute COVID-19 in High-Risk Patients.

Faculty and Disclosures

I am Michele Bartoletti. I am Associate Professor of Infectious Disease at Humanitas University and Head of Infectious Disease at Humanitas Research Hospital in Milan, Italy.

And you can see my conflict of interest in this slide.

Learning Objective

So the learning objective of this educational program is to formulate strategies to employ timely outpatient COVID-19 treatments for patients at risk for severe disease or complications.

Patient Case 1

I will start with a clinical case very common in our hospitals. So this is a 52-year-old man who reports to urgent care with shortness of breath and fever. He reports that symptoms started about a week ago. His past medical history includes COPD, hypertension, hyperlipidemia and treatment with simvastatin. He performed a rapid test that is positive for SARS-CoV-2.

Burden of COVID-19 Severe Disease

I will start talking about the burden of COVID-19 severe disease in this population. So I think when we talk about COVID-19 in 2026, we probably have to remember that COVID-19 is not only responsible for severe pneumonia, but also for exacerbating the underlying medical condition.

So what we currently see in our hospitals is that a lot of patients come in with not the pneumonia that we've seen during the pandemic, but we still see many patients, especially patients with a large number of comorbidities or elderly patients—an immunocompromised patient that is experiencing some exacerbation of underlying medical condition.

Sometimes we can see patients with advanced infection processes such as persistent viremia, long COVID, or persistent COVID, and patients with secondary bacterial infection. And all of this burden of COVID-19 is responsible for increased mortality and morbidity, especially hospitalization and death in the vulnerable population.

Antiviral Options for COVID-19

We have a lot of antiviral options for COVID-19. And we have remdesivir, nirmatrelvir/ritonavir, and molnupiravir as antiviral in the majority of our countries.

Remdesivir

And remdesivir is an antiviral that inhibits viral replication. It is administered as intravenous treatment. And the treatment duration is 3-10 days, depending on the kind of symptoms and the severity of patients and the setting of care, like in inpatient vs outpatient.

It has no or maybe very little drug-drug interaction, and maybe it can cause hypersensitivity, but this is not common. And it can be avoided just slowing down the infusion. And this can be helpful for reducing the hypersensitivity.

Remdesivir: Place in Therapy

Generally, we use as an inpatient use, but we have some very favorable data of outpatient use. For example, the PINETREE trial, which was published in New England Journal of Medicine, said that if we start remdesivir within 7 days of symptom onset compared to placebo, remdesivir may be responsible for lower risk of hospitalization or death.

So currently, guidelines suggest to use remdesivir inpatient with this kind of condition. So within 7 days of symptom onset and as 3 day treatment, especially in the outpatient setting.

Nirmatrelvir/Ritonavir

Nirmatrelvir/ritonavir is another available option; it is a very good drug that inhibits viral replication. It has a good advance because—we say it is a good option because it can be administered orally. The treatment duration is 5 days but unfortunately has some very important drug–drug interaction, especially because ritonavir is a strong inhibitor of CYP3A4, and generally these increased levels of drugs that are metabolized by the same cytochrome.

So because the drug can affect the metabolism of many other drugs, we have to be very careful when we use this drug with the concomitant drugs.

Nirmatrelvir/Ritonavir: Place in Therapy

So generally, nirmatrelvir/ritonavir is primarily used in the outpatient setting; it is indicated for mild to moderate COVID-19 disease in adults who are high risk for progression to severe COVID-19. It has to be started within 5 days of symptom onset. And we have to increase public awareness about the drug that may be beneficial for patients.

The phase II/III randomized controlled trial showed that decreased hospitalization and death in patients treated with nirmatrelvir/ritonavir compared to placebo, especially when they were treated in the first 5 days of symptom onset.

Molnupiravir

Another good option is molnupiravir, another antiviral that inhibits viral replication. It has to be administered orally bis in die, and treatment duration is 5 days. It has no significant drug–drug interaction, but unfortunately has potential for teratogenic side effect, so it is not recommended in pregnancy.

And we have to be cautious when we use in males and females with potential for a productive reproductiveness.

Generally, it has some side effects, including GI upset and dizziness.

Molnupiravir: Place in Therapy

And in terms of efficacy, it is an alternative option to other agents when these are not appropriate and have to be started within 5 days of symptom onset. There are some conflicting results from clinical trials. Some trials show that it can reduce the risk of hospitalization and death from COVID-19, but other randomized controlled trials have demonstrated no efficacy, especially when it was used in the later phase of the pandemic. So when the patients were highly vaccinated or has a lower number of comorbidities.

Combination Antiviral Treatment (Off-label)

There are also some good studies, observational studies, or randomized controlled trial that compared monotherapy vs combination, and especially in immunocompromised patients, remdesivir plus nirmatrelvir/ritonavir has demonstrated very good efficacy in reducing the potential for mortality of very severe disease in immunocompromised patients.

There is an ongoing randomized controlled trial which may determine the superiority of combination treatment vs monotherapy in this setting. At the moment, there's no clear recommendation in the

guidelines because there's no randomized controlled trial. But there are some consensus documents that say, especially in immunocompromised patients with severe disease and progressive disease, this could be a good option for this setting.

Benefit of Early Outpatient Antiviral Treatment

And especially, we have to remember that antiviral treatment has a specific window of opportunity, which is in the first 5–7 days of treatment—of 7 days of symptoms onset. And this is because the pathophysiology of infection caused by SARS-CoV-2 is very clearly described in the literature.

We have a very early infection, which we have a strong viral replication. Then we have the pneumonia pulmonary phase when there is the onset of pneumonia. And then we have a hyperinflammation phase, which is typical for patients with severe disease undergoing mechanical ventilation and having septic shock.

In this case, antivirals are less effective compared to early phase of the disease. And in this phase, probably anti-inflammatory drugs are very, very helpful for treating patients.

Patient Case 1: Discussion

So going back to our patient case 1 and discussion about this patient. Please remember that this was a 52-year-old man with the urgent need for urgent care and shortness of breath and fever. His past medical history was about COPD, hypertension and hyperlipidemia with ongoing treatment with simvastatin. And the patient tested positive for SARS-CoV-2.

Our choice was remdesivir. And we think that this is the best option for this patient because of high efficacy, as demonstrated before. No drug–drug interaction. And because the patient has symptom onset to 7 days before. So if you remember, remdesivir can be still effective when used within 7 days, compared to nirmatrelvir/ritonavir that should be used in the first 5 days of symptom onset and has potential for drug–drug interaction, especially with simvastatin.

This is not a very big deal in this specific patient, because we can discontinue simvastatin for a few days and then restart the assumption of simvastatin. However, we cannot use properly nirmatrelvir/ritonavir because the symptoms onset was 7 days earlier.

Key Points

So the key points. The choice of antiviral for COVID-19 requires the following assessment. One is patient location, inpatient vs outpatient. And we have to take into account our organization or our logistics of our healthcare. So if we have the opportunity in our hospital or outpatient clinics to do intravenous treatment, we can use remdesivir even as an outpatient or, unfortunately, we don't have this kind of facilities, we are forced to do an oral antiviral.

We have to take into account the risk of progression to severe disease. So remember that immunocompromised patients and patients with multiple comorbidities are those with higher risk to develop severe disease. Obviously we have to be careful about drug–drug interactions, especially when we use nirmatrelvir/ritonavir. And also some counseling point results of clinical trial, condition of patients, severity and nonsevere patients, geographic availability.

Because please remember that molnupiravir, for example, is not available in many countries like my country, like in Italy, unfortunately, we don't have molnupiravir anymore. So our choice will be between nirmatrelvir/ritonavir and remdesivir.

Go Online for More Coverage of COVID-19

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Thank you so much for your attention.