

COVID Rounds: Management of Severe COVID-19 in People Who Are Immunocompromised

Introduction

Dr Cristina Mussini (University of Modena and Reggio Emilia):

Hello, everybody. Welcome to this educational program titled, Covid Rounds: Management of Severe COVID-19 in People Who Are Immunocompromised.

I am Cristina Mussini, Professor of Infectious Diseases, and Director of the Clinic of Infectious Diseases at the University Hospital of Modena, Italy.

Joining me on this roundtable discussion, there are 2 colleagues of mine who are:

Dr Michele Bartoletti (IRCCS Humanitas Research Hospital):

Hello, I'm Michele Bartoletti, Associate Professor of Infectious Diseases at the Department of Biomedical Science of Humanitas University, and Head of Infectious Diseases Unit at the Humanitas Research Hospital in Milan, Italy.

Dr Martin Witzernath (Charité - University of Berlin):

And my name is Dr Witzernath. I'm Professor and Chair for Respiratory Medicine and Critical Care at the Charité University Hospital in Berlin.

COVID Burden

Dr Mussini:

So let's start talking about the COVID burden in immune compromise, because this is the topic of this roundtable.

INFORM: COVID-19 Outcomes in Immunocompromised and Other High-Risk Populations in UK

There is an important cohort. The immunocompromised individual was 3.9% of the study population. So the outcome was in 500,000. And these 500 were 3.9% of the study population.

If we look at the percentage, the percentage is low. But if we look at the rate of hospitalization, we see that this population accounted for almost 22% of hospitalizations, almost 25% of those who had more than 3 vaccinations, but especially 24% of death. Among the deaths, 25% of the deaths were fully vaccinated with more than 3 doses.

INFORM: COVID-19 Outcomes by Population

So looking at the risk of hospitalization or death, you see that among the immunocompromised, all immunocompromised have an increased risk compared to those who are not immunocompromised.

But we have to underline that especially those who underwent hematopoietic stem cell transplant within 2 years, or those with solid organ transplant, and especially on antirejection drugs, they really had a much higher risk, not only of hospitalization, but especially of death.

Multiple Factors May Affect Vaccine Efficacy in CLL and Other Lymphoid Malignancies

Why this if one fourth of those who were hospitalized and one fourth of those who died were fully vaccinated? Because among people who are immunocompromised, and especially among those who have a hematological disorder, we know that there are multiple factors that may affect vaccine efficacy.

In this slide, we see those who have a chronic lymphocytic leukemia or other lymphoid malignancies that were studied and published in this paper.

You see that there are vaccine factors, those intensity and frequency. We are talking about 3 doses, but since we know that the response to vaccination fade with the time, we know that it's important that these people continue to vaccinate themselves, so 3 maybe are not enough.

There are also patient factors like age, comorbidities, hypogammaglobulinemia, but also treatment factors, for example, not seeking for treatment as soon as possible. So doing something like watch and wait, or having been previously treated, or having active treatment that can reduce either hospitalization or mortality.

Of this reduced number of people mounting an immune response, there is still a question of antibody titers. This because it's not only about the quantity of antibodies, but especially about the quality of the antibodies in order to understand if they are neutralizing antibodies, really protective one or not, and the persistence of the defense.

So that's why we can have, when all these factors work in the right direction, a reduction in the clinical incidence of the infection. But if some of these situations don't go in the right direction, we have an increased risk of hospitalization and of death.

Initial Framework: Determining COVID-19 Severity and Risk Factors for Progression

Dr Witzernath:

So let's go to our patient.

Patient Case

The patient that we see here is a 45-year-old woman with a recent diagnosis of mediastinal lymphoma that is admitted for febrile neutropenia, mucositis, and acute respiratory failure. She reported URI symptoms with coughing and sore throat that began 2 days ago.

The vitals are a temperature of 38 degrees Celsius. Blood pressure is 130 over 85. Heart rate is 90 beats per minute. The respiratory rate is 24 breaths per minute and the saturation is 89%, resting on room air. Her home medications were EPOCH-rituximab that she received with the last cycle 2 weeks ago. Acyclovir, fluconazole and levofloxacin, and trimethoprim/sulfamethoxazole.

Her vaccination status was a completed initial mRNA series that was boosted in 2021, and she had COVID-19 in 2022, so 2 years ago. Now her COVID-19 antigen test is positive and she has been initiated on IV vancomycin, cefepime, and micafungin for febrile neutropenia and acyclovir is continued.

So the question here is now, should any COVID-19 therapies be initiated?

COVID-19 Diagnostic Workup

First of all, of course, we need a complete diagnostic workup for the COVID-19 disease. This includes the standard history and physical to assess the severity of the disease and risk factors for progression to severe COVID-19; I'll go into details of this in a minute.

Lab testing has to be completed. We need a PCR for SARS-CoV-2 and a CBC with a differential and a CMP and maybe other labs as appropriate regarding her comorbidities.

With respect to imaging, chest x-ray needs to be done, and I personally strongly suggest to do a low-dose chest CT scan in these patients. We need an EKG, and again, depending on the comorbidities of this patient, other studies.

Assessing for Clinical Severity and Worsening

Now how do we assess clinical severity and the probability for worsening? Of course it's important to look at the qSOFA criteria that we always use in patients with infectious diseases presenting to the hospital. So is there a new onset of confusion? Does the patient have respiratory rate equaling 22 breaths per minute or more? Is the systolic blood pressure below 100 millimeter mercury or the oxygen saturation below 92%?

This is particularly important in patients with COVID-19 because they very frequently experience what we call happy hypoxia, which means that they have low oxygen saturation, but they do not suffer from it, so they do not increase their respiratory rate. Therefore, it's important to measure to quantify oxygen saturation in these patients and not only measure the obviously very important respiratory rate.

We also look for pCO₂ if we have a blood gas analysis, because patients who are breathing more have lower pCO₂ values. And we look for a serum lactate, because increased serum lactate is a bad predictor or predictor for unfavorable trajectories.

We also check for acute renal failure for specific comorbidities like pulmonary or cardiovascular or other comorbidities, and of course, for severe immune suppression.

Regarding these diagnostic considerations, I would like to ask my 2 colleagues how to determine if the patient is getting worse and what to do. What do you usually do, Michele?

Dr Bartoletti:

This is a great question. I think what you already show is very important. I think that the first of all, clinical evaluation is much important for these patients. So we have to check everything that can be foreseeable for a worsening condition for this patient.

Obviously, past medical history is very important because we know that some immunocompromised patients have a higher risk for developing severe condition or progress to critical condition as well.

Then in terms of labs, I think that inflammatory markers could be a good option. So we know that there's a lot of literature talking about CRP, about procalcitonin as well, even though we know that we use this to differentiate between patients with the bacterial coinfection or superinfection.

We can use interleukin for assessing the severity of the patient. But I think that the best way, again, is to assess normal SOFA score, qSOFA sometimes, and all the features that you already shown in the previous slide.

Dr Witzenrath:

Cristina, would you like to add anything?

Dr Mussini:

Yeah. Obviously the clinical examination is the most important, but if the clinical examination is not so clear that the patient will - did not show clearly that the patient will progress. We look at the CRP, I have to say. Sometimes you have a sort of contradiction between the clinical picture and a CRP that is increasing. These are people who can have a bad prognosis.

Also when you have to decide when to use, for example, we will talk about treatment but also immune modulator. I think that CRP is very easy. It's cheap and it's something that is in our routine. While for example, IL-6, you know, is not; we don't have a real cut off. For CRP, we have some values from the trials that were conducted during the first waves.

Probably they are not the same in immunocompromised in the Omicron era, but still as all the markers, I think that the trend is the most important. If you see an increase, it's something that I would have a look on.

Dr Witzenrath:

Now, the 2 of you are great experts in ID. Is there any use in consulting other disciplines, maybe critical care or any other?

Dr Bartoletti:

Absolutely, yes. I think that the decision of any treatment and program for the patient should be shared with all members and all, I would say, main character of the patients. What does it mean? If we are talking about immunocompromised patients. So I think that the decision on the type of treatment and the pathway that the patient should follow should be shared with, for example, hematologist or a solid organ transplant unit specialist, intensive care unit specialist. Because I think all together, anyone can give very important information and very important skills for the good of the patient. So I think the multidisciplinary approach is very, very important in this case.

COVID-19 Treatment Recommendations

Dr Witzenrath:

So maybe we move on. And before we step into treatment of COVID-19, it might be useful to briefly recall the normal trajectory of the COVID-19 disease upon SARS-CoV-2 infection.

Management Strategies for COVID-19 Infection

This is illustrated here. Of course, you all know that after the infection, people are infectious even before symptoms start. And at that time, they are asymptomatic. But then symptoms may start with mild symptoms. In the worst cases, these patients may experience a trajectory to moderate and even severe disease states, where the SARS-CoV-2 RNA is usually going down to low levels in the moderate and severe disease states.

However, particularly in immune-incompetent patients, the SARS-CoV-2 RNA levels may stay relatively high. And we will have to discuss this with respect to treatment options.

Now, the normal or usual care of patients with symptoms is: in outpatients, that you can consider to give antivirals, and in those with moderate or severe disease, also in inpatients, antiviral therapy may be your choice alongside with potentially with immunomodulators, depending on the patient on the severity of the disease and on the question whether the patient is immunocompetent or immune-incompetent.

NIH COVID-19 Guideline Recommendations

And if we look into the NIH COVID-19 guideline recommendations, here we see that in the ambulatory setting, in patients who are treated as outpatients or are hospitalized for non-COVID-19 reasons but have a positive COVID-19 or SARS-CoV-2 PCR, steroids are not recommended and antivirals are recommended in patients that are at high risk of progression and then only within 5 to 7 days of symptom onset, for example, nirmatrelvir, ritonavir, or remdesivir. Molnupiravir could be an alternative.

In hospitalized patients without oxygen, again, steroids are not recommended. Again at high-risk of progression, remdesivir is recommended in hospitalized patients that need oxygen or are on high-flow oxygen or noninvasive mechanical ventilation, dexamethasone and remdesivir are recommended in the NIH guidelines.

In hospitalized patients in the ICU on mechanical ventilation or on extracorporeal membrane oxygenation, remdesivir treatment can be considered in patients who are immunocompromised and have evidence of ongoing viral replication, or less than 10 days since symptom onset.

Immunomodulators can be considered like baricitinib or tocilizumab, and in these patients who are hospitalized and need oxygen and have high inflammatory responses. Anticoagulant recommendations are given by the NIH for hospitalized patients, but be aware of the risk of negative effects when patients in the ICU are treated with therapeutic anticoagulation.

IDSA COVID-19 Guidelines Recommendations for Hospitalized Patients

Regarding the IDSA COVID-19 guidelines, again, severity of illness is important, and in those patients who have mild to moderate COVID-19, no steroids are recommended. And again, those patients with a high-risk for progression to severe disease. Within 7 days of symptom onset, remdesivir is recommended.

You may consider also nirmatrelvir/ritonavir as an alternative, if the patient is within 5 days of symptom onset. In severe cases and in critically ill patients, dexamethasone is recommended. And in the severe cases, there's also remdesivir recommended. In both severe and critically ill patients with elevated markers of systemic inflammation, baricitinib or tocilizumab can be used.

Comparing Guidelines

Now, when we compare the guidelines for severely ill patients who are either on high-flow oxygen or noninvasive mechanical ventilation, remdesivir plus dexamethasone are recommended by NIH, IDSA, and WHO guidelines, as long as these patients are immunocompromised or at high risk of severe disease progression.

Patients with invasive mechanical ventilation or on ECMO, again, if they are immunocompromised, they should receive dexamethasone. Not all guidelines recommend remdesivir in this case, but a number of NIH panel members recommended to add remdesivir to these patients with invasive mechanical ventilation, or on ECMO who are immunocompromised—immunocompromised patients who have ongoing viral replication or are within 10 days of symptom onset.

Antiviral Therapy

Dr Bartoletti:

Yeah, we already talk about antiviral treatment when we talk about guidelines, of course. But in the next few slides, I think we're going to try to focus more on antiviral treatment to see what - what are the results of main clinical studies.

SOLIDARITY: RSV for 10 Days vs Control for COVID-19 in Hospitalized Patients

So the first study we would like to show you is the SOLIDARITY trial. SOLIDARITY was a large trial that assessed a large number of drugs. It was very important because it helped us to differentiate which type of drugs are very useful and which should be avoided. For example, I remember that SOLIDARITY assesses hydroxychloroquine, azithromycin, interferon that are not used anymore.

It also assesses the use of remdesivir vs control for hospitalized patients with COVID-19. And the first part of the trial, it was very surprising, in my opinion, that the trial did not show any benefit in terms of outcome of patient treated remdesivir with and vs control.

However, after they complete the whole study and they do also meta-analysis with the other of the trial, this trial was able to show an important benefit of remdesivir vs control.

I think that the results should be commented, because if I remember, in my center, for example, we participated in the SOLIDARITY trial. And I remember that patients that were there were [inaudible] patient that were hospitalized recently. But in that way - in that part, on that wave and that in our organization of healthcare, I remember that patient that we hospitalized were very advanced because they stayed at home for a long time with no treatment, and only when they became very, very critical, I would say, they get to the hospital.

So we have to remember that these patients were enrolled in the first randomized, controlled trial using antivirals. And we know that because Martin already showed that antivirals are very effective in the very beginning of the disease, because in the very beginning we have a high viral replication.

So however, when the whole database was assessed with more 88,000 patients, this trial demonstrated a benefit in the use of remdesivir vs control in hospitalized patients with COVID-19.

Remdesivir for Immunocompromised Patients Hospitalized With COVID-19 Across Variant Waves in US

Beyond a randomized control trial, the SOLIDARITY is not the only one. We have a lot of other trials. There's a lot of real-world evidence data. This is a retrospective study using the PINC AI database, which is a large database in the US. And this study enrolled nearly 30,000 patients. So it's very huge in terms of amount of data.

And this study was also focused on immunocompromised patients. What we see is that across the variants, the multiple waves of variants in the US, remdesivir use was associated with lower 40-day and 28-day mortality compared to controls that are patients that were not treated with remdesivir.

Dexamethasone

Beyond remdesivir, we all are antivirals. We should talk about dexamethasone or immunomodulating drugs.

Remdesivir + Dexamethasone vs Dexamethasone Alone for Patients Hospitalized With COVID-19 in US

So we know that dexamethasone should be used in patients requiring oxygen, but we know that when this drug was starting to be used in the very beginning, a lot of patients, even without oxygen were treated with dexamethasone because most clinicians wanted to treat the patient very much.

We know that according to the trial that demonstrated the benefit of dexamethasone, patients not receiving supplemental oxygen had higher mortality when they were treated with dexamethasone. And this is paradoxically, that patients that require low- or high-flow oxygen received a benefit in terms of outcome when they were treated with dexamethasone.

This is another study showing that the patients who received dexamethasone even with no need for supplemental oxygen, but they were also treated with antivirals, show a - receive a very important benefit from antivirals, reducing the mortality compared to controls that were treated with dexamethasone alone. So the message that we would like to give is that if we wanted to use dexamethasone, even though this is not recommended by guidelines, please remember to use also an antiviral because this could decrease a lot of the mortality for COVID-19.

EPICOVIDEHA: Dexamethasone for COVID-19 in Patients With Hematologic Malignancies

EPICOVIDEHA, which is a large database of patients with COVID-19 and hematologic malignancy that enrolled nearly or more than 1000 patients with these conditions, and they do an analysis about the use of dexamethasone in these patients. And this is very interesting.

As you can see, this analysis was about 500 patients receiving dexamethasone and 470 patients receiving dexamethasone plus antivirals. These patients were hematologic patients with a different and heterogeneous type of conditions.

EPICOVIDEHA: 90-Day Mortality by Treatment

As you can see when the patient is receiving dexamethasone alone, there was a mortality that was higher when compared to dexamethasone plus antivirals.

EPICOVIDEHA: Survival By Treatment

These results are also shown better in this Kaplan-Meier curve. As you can see, when they stratify the patients that were at home, hospitalized but not in the ICU, or even hospitalized in the ICU, they found a benefit among patients that were receiving dexamethasone plus antivirals when compared to antivirals alone or dexamethasone alone.

So remember that if you wanted to use immunomodulators, especially in the immunocompromised patients, remember to use also an antiviral, because this is very important for this kind of group of patients.

We know that immunocompromised patients already have a condition that theoretically should lower the inflammatory response to viral, bacterial, or fungal infection. So what do you think about the use of dexamethasone in this group of patients? Should it be avoided, or we can use it but with concomitant antiviral? Or there is a space on this type of drugs alone without antivirals? What's your opinion?

Dr Witzenrath:

I would not say that we have to avoid dexamethasone in every patient that is immunocompromised. Obviously, there are situations in which these patients may benefit from dexamethasone, for example.

Nevertheless, the data are very scarce on this. And of course, we have to use it with a lot of caution. And this is what you very nicely just demonstrated on the basis of clear data, that we should be very careful with dexamethasone in severely immunocompromised patients and only a very small portion of these patients may benefit from dexamethasone.

And particularly in COVID-19, these patients then obviously need antiviral therapy alongside or even without dexamethasone.

Dr Bartoletti:

Cristina?

Dr Mussini:

I think that in this patient, it's very difficult to use only dexamethasone without the antiviral because as we think about the different phases, we know that the viral phase lasts much more than in immunocompetent.

So usually, even in more advanced patients, we use antiviral. So I don't think that there is the need to use dexamethasone without antiviral. So we first start with antiviral. And if it doesn't work, we add dexamethasone.

So I'm very cautious about dexamethasone because I've been burned as all of us at the beginning where they say that, during MERS, dexamethasone was counterproductive. And so we didn't use it. And then the RECOVERY trial showed that it was beneficial.

So I would not say that from one study there is some low, you know, carving the stone. I think that it's good to use. You know, it's a weapon that we have. I don't think that it's really something that, as you said, should be avoided. I would not say this.

Dr Bartoletti:

Dr Witzenrath?

Dr Witzenrath:

We should elaborate a bit more on that and differentiate between, you know, mildly or moderately immunocompromised patients and then those with really severe immunocompromised situation. Because even if you have not so many but still some neutrophils and T-cells and so on, they can get mad and really have a hyperinflammatory situation in which you would like to give dexamethasone or an immune response that does not resolve over time, for example, because there is also still virus there. In this situation, it might sometimes be beneficial, but again, with a lot of caution.

Dr Mussini:

And we know also that steroids can represent a risk factors for fungal infection in this patient. So it's a clinical picture that is very complicated. But I would not say yes or I would not say no. I would say that probably in this patient we use everything that we have if the clinical picture is getting worse rapidly. So I would not say that someone would, you know, say no, no, never dexamethasone.

Dr Bartoletti:

Yeah. It's true. And I think that as Martin said, it's very important. I think, that the group of immunocompromised patients is very heterogeneous. So we generally consider immunocompromised patients and neutropenic cancer—hematological patients or transplant patients or even patients with cancer receiving chemotherapy.

I think that these 2 groups are very different from each other. And probably dexamethasone in the cancer patients could still be beneficial. But I don't think that in hematologic patients with a completely neutropenic patient is still important.

So I think that we have to differentiate a lot between the whole group of immunocompromised patients. And I think that probably in this group, especially very, very immunosuppressed, the dual antiviral therapy or combination antiviral therapy could be a good weapon when - when they not respond or even when they start with the critical condition, because there are a lot of case series and case reports showing that there is a lot of beneficial.

And I think also from - from my clinical perspective and experience, they respond very well when we start dual antiviral treatment.

What do you think about this and do you have experience on that in - in your setting - in your hospital?

Dr Mussini:

Yeah, I mean, it was what I was saying when I said we use everything that we have. I mean, I think that we - we use also dual antiviral therapy in order to get rid of the - a positive swab and - and maybe they - because they have to undergo chemotherapy, for example, but also in those who are, you know, where their immune system is really zero and you need any weapon in order to, you know, defeat the virus. And you know that they don't have lymphocytes. They don't have neutrophils, they don't have cells. So it's better to use all the antivirals that we have.

So dual antiviral is absolutely something that we have used in a few patients—fortunately in a few patients. It's not something that we have to do to everybody.

Other Immunomodulators

So we already mentioned many times the immune modulators. And so among the other immune modulators, we have 2 groups. One is the JAK inhibitors, and we are talking about baricitinib and tofacitinib. And IL-6 inhibitors, tocilizumab and sarilumab.

Baricitinib for Severe COVID-19: Select Phase III Studies

So baricitinib. Why baricitinib? Baricitinib, because it's easy to take, it's oral. It's not very expensive. So I think that it has several opportunities to be used. And it's used and its recommendation is based on some phase III studies. So the 3 studies were COV-BARRIER, COV-BARRIER-2 and RECOVERY.

The population were all hospitalized. In the COV-BARRIER, we are talking about more than 1500 patients, 79% on steroids. The rate of progression to respiratory failure and to death did not differ between baricitinib and placebo, even if there was a trend because it was lowering baricitinib, it was 28% vs 31% in placebo, but it was not statistically significant.

What differs? It was the 20-day all-cause mortality. So I think that this is a very good result. Another double-blind placebo-controlled was the COV 2 that was in much less patients, but they were in invasive mechanical ventilation or in ECMO. And again, 20 days all-cause mortality was lower with baricitinib, 39%, vs placebo, 58%. And the risk reduction was 46%.

The RECOVERY, it was an open-label because it's the adaptive platform from UK. And it was baricitinib plus standard of care vs standard of care, more than 8000 patients. The 20-day all-cause mortality was lower with baricitinib because it was 12% vs placebo 14%. And there was a 13% mortality reduction with baricitinib.

STOP-COVID: Tofacitinib for Severe COVID-19

The other drug for severe COVID-19 is tofacitinib. It was studied in Brazil, and it's very expensive that's why we don't use it routinely. At least in Italy, we never used it. And what we can see is that in Brazil, in this multicenter, double-blind, placebo-controlled trial almost everybody received glucocorticoids, almost 90%, but the severity of the disease was very heterogeneous because 25% were not receiving oxygen, 63% were on a low-flow oxygen, and 13% on high-flow oxygen.

As you can see, the risk reduction of having death or risk of death and respiratory failure at Day 28 was 37% reduction in those using tofacitinib compared to placebo. You know, we will discuss it. I think that it's important to really select where the population and probably at the end of all of these studies, we don't have a single study that could have where we could see the real benefit of any of these anti-inflammatory drugs because the results are very heterogeneous.

Tocilizumab or Sarilumab for Severe COVID-19

There was also a meta-analysis. You know, all these meta-analyses, all these comparisons among trials really are led by some of them. We have seen all the meta-analysis on tocilizumab before the RECOVERY trial that showed that there was not a big benefit. After the RECOVERY trial, there was a benefit. So it's important to put all them together. And we are talking about a meta-analysis of 36 trials, 20 trials on tocilizumab, 7 trials on sarilumab. So almost 20,000 people with COVID-19.

Use of tocilizumab or sarilumab with corticosteroids was associated with lower mortality rates, but maybe less beneficial without corticosteroids. But at this point, after the first RECOVERY trial, the standard of care, there was also corticosteroids.

And you see that tocilizumab plus corticosteroids vs corticosteroids alone was 0.79. And sarilumab plus corticosteroids vs corticosteroids alone was 0.73.

Patient Case

Dr Bartoletti:

So we go back to our patient case. The 45-year-old woman with the recent diagnosis of mediastinal lymphoma, admitted for febrile neutropenia mucositis. Remember that she was febrile with an oxygen saturation of 89% resting on room air.

She initiated vancomycin, cefepime, and micafungin. She was positive for COVID-19 on antigen test. Should we start any treatment for this patient against COVID-19?

I will start discussing this case. Obviously, I think we should start treatment for COVID-19 because of the severity of condition, because she is immunocompromised and she is neutropenic. So there is a clear benefit in using antiviral first step for this kind of patient.

I would personally start remdesivir because she is hospitalized. And this is the preferred drug for hospitalized patients. Remember that nirmatrelvir/ritonavir could be used also. But probably when the patient has an IV, we would prefer to use remdesivir because the benefit is similar.

But we have a lower rate of adverse events and a lower rate of drug-drug interactions when we use remdesivir compared to nirmatrelvir/ritonavir.

I think we should also assess for bacterial superinfection, or even fungal superinfection because we have a patient with febrile neutropenia. So I will probably be careful to search for additional coinfection superinfection.

And I will assess the clinical outcomes to see if the patient may benefit from adding another antiviral or even in a second step, immunomodulating drugs.

What do you think, Martin? Would you do the same or something slightly different?

Dr Witzenrath:

Yeah. No, I fully agree regarding antiviral and antibacterial antifungal therapy. Regarding anti-inflammatory therapy, I mean, Cristina nicely showed all the data of the trials. But I think we have to consider that these trials included also immunosuppressed patients, at least some of them.

But of course, this was only a very minor share of patients in these trials, and I'm not aware of specific data showing that immunosuppression with tocilizumab or baricitinib or one of the other drugs that we discussed is in the same way beneficial in immunocompromised patients as it is in immune-competent patients. And I think we have to—as we discussed for dexamethasone— have to be cautious with anti-inflammatory therapies in immunocompromised patients.

Do you think in the same way, Cristina?

Dr Mussini:

Yeah, definitely. Yes. Definitely, yes. Completely agree. I - you know, it's not only I think that - you know, we - we say that the - or not - I mean, IV remdesivir, but also there are maybe some drug-drug interactions because she will be put also in antifungal therapy in other situations.

So I think that nirmatrelvir/ritonavir will be difficult to be prescribed in this woman. But no, I totally agree with what you said. And we have to consider that all the data that we have seen were not specifically, as you said conducted in severe immunocompromised patients. So we don't have the evidence in these patients, a clear evidence of how, for example, immune modulators can work in these patients.

So it's - but for sure, if the clinical picture will deteriorate, I would use also immune modulators.

Dr Bartoletti:

What do you think the current guidelines can give us all important information for the management of this kind of patient? Or they are more focused on normal standard patients? Because I think that this discussion was very broad and will include a lot of things that are not included in the current guidelines.

So I think that what they did in Germany that they would ask me. We are trying to do a consensus for document for immunocompromised patients. Because I think that current guidelines do not help us much in this specific setting. What do you think?

Dr Witzenrath:

Yeah.

Dr Mussini:

No, no, I completely agree.

Dr Witzenrath:

Yeah, I'm very much looking forward to the ESCMID guidelines on immunocompromised patients.

Dr Mussini:

Also because you know the guidelines rely on the evidence. And it's difficult to conduct a trial on - on this specific population. So it's difficult.

Dr Bartoletti:

Yeah, I fully agree on that.

Key Take-home Points

We have to discuss some important take-home points. So I think that treatment of COVID-19 hospitalized patients depends on host, severity, availability of drugs, condition, program for the immunocompromised patients, and especially in terms of which kind of treatment the chemotherapy transplant they have to follow for the underlying disease.

I think that remdesivir is the most beneficial, especially in this group of patients, hospitalized patients and patients who are critically ill. There is still a large debate, I think, in immunocompromised patients receiving immunomodulators. There are experts that probably still consider immunomodulatory drugs for the immunocompromised patients. But we also have to consider which kind of immunocompromise, because we know that we are talking about a very heterogeneous group of patients going to a mild patient with solid cancer receiving immunotherapy or a chemotherapy to patients who are transplanted or receiving high-dose chemotherapy, or patients with febrile neutropenia with leukemia.

So I think that's a very broad group of patients that in some group probably immunomodulators are still useful, but in others probably immunomodulators are not useful anymore. And also probably antiviral treatment in these patients is very important. We should consider that initially to start the - at the very beginning antiviral treatment. And consider also dual antiviral treatment, especially in patients will not improve early during the course of the first round of treatment.

So I think we concluded with this webinar. It was a pleasure to be with you today and with my colleagues, Martin and Cristina. So thank you so much for your attention.