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Insights from Experts: Preventing and Managing CMV Post-Solid Organ Transplant

Announcer:
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Dr. Silveira:
Hello and welcome to Insights from Experts: Preventing and Managing CMV Post Solid Organ Transplant. My name is Fernanda Silveira, and I'm a Professor of Medicine and Director of Clinical Operations for Transplant Infectious Diseases at the University of Pittsburgh and UPMC. I am joined today by Dr. Jennifer Saullo, Transplant Infectious Diseases Specialist and Associate Professor of Medicine at Duke University.

We have a full program for you all today. I will start off with a presentation on CMV prevention and treatment in solid organ transplant, and next, Dr. Saullo will talk about refractory and resistant CMV in solid organ transplant. Then we will go over some cases to help bring everything together.

So let's start with CMV prevention and treatment in solid organ transplant. CMV is a virus with a high seroprevalence. In developed countries, about 60% of adults are seropositive for CMV. And CMV establishes latency. This high seroprevalence and the latency makes CMV one of the most common opportunistic infections in solid organ transplant recipients. It is associated with high healthcare utilization and costs, because it adds to hospital days, to hospital readmissions, and hospital costs. It causes direct effects via CMV infection and CMV disease, as well as some indirect effects, such as increasing the risk of acute and chronic rejection, increasing the risk of bacterial, fungal, and other viral opportunistic infections, the risk of PTLD, as well as adding to mortality.

When we talk about CMV, it's important to differentiate between CMV infection and disease. When we refer to infection, we're talking about evidence of CMV replication in tissue, blood, and other bodily fluids, without the presence of symptoms. The CMV replication is detected by nucleic acid or antigen testing. CMV disease, on the other hand, refers to CMV infection plus signs and symptoms. And we can have two different presentations, CMV syndrome, which is characterized by fever, malaise, presence of atypical lymphocytes, leukopenia, or neutropenia, thrombocytopenia, transaminitis; or CMV tissue invasive disease that can manifest in different ways, including but not limited to GI disease, pneumonitis, hepatitis, nephritis, and retinitis.

The most important risk factor for CMV disease is the CMV serostatus of the donor and the recipient. With patients who are CMV donor-positive, recipient-negative, having the highest risk for CMV disease. The type of transplant also influences the risk, with patients who have received lung and intestinal transplants having a higher risk of disease as compared to other transplants. Other risk factors include the net state of immunosuppression, acute rejection, and advanced age because of immunosenescence that is associated with it.

We currently have two strategies to prevent CMV, universal prophylaxis and preemptive therapy. Universal prophylaxis refers to the administration of an antiviral with anti-CMV activity to all patients at risk for CMV for a defined period of time after solid organ transplant. In prophylaxis, antiviral is started immediately after transplant and no later than 7 days post transplant. Preemptive therapy, on the other hand, refers to starting antiviral therapy only for patients who demonstrate evidence of CMV replication.

We now have a question for you. When it comes to CMV prevention, which of the following do you find most challenging?

This table compares universal prophylaxis to preemptive therapy. In terms of efficacy in preventing CMV disease, both of these strategies are effective. With universal prophylaxis, early CMV infection is uncommon, while it is common with preemptive therapy. Universal prophylaxis is easy to implement. You start your antiviral medication and you continue for the time you determine appropriate. Preemptive therapy, on the other hand, requires a lot of logistics.

Now let's review the current CMV antivirals. This table shows the current antivirals with activity against CMV that we have available. And there are a few things that I would like to point out. First, if you look at the CMV target, the four first antivirals that we have on this list have the same target, which is the DNA polymerase, which is encoded by the UL54. The most recent drugs, maribavir and letermovir, are the ones with a different target for action.

The other thing to point out is that we only have three drugs that are available with an oral formulation, valganciclovir, maribavir, and letermovir. And lastly, these drugs have different indications approved by the FDA, with some of them being approved for prevention and treatment, and others only for treatment, with more recently, letermovir being approved for prophylaxis, but only in high-risk kidney transplant recipients.

Now, looking again at the antivirals, it's important to understand their toxicities and limitations. The first thing that I want to point out is their activity against herpes simplex and VZV. Only ganciclovir, valganciclovir, foscarnet, and cidofovir are active against these other herpes viruses. This is important, because if your patient is considered to be at risk for reactivation of one of these viruses and they are not on one of these drugs, they will need additional prophylaxis with acyclovir, valacyclovir, or famciclovir.

Looking at toxicity, valganciclovir and ganciclovir are associated with bone marrow suppression. Foscarnet is associated with kidney injury and electrolyte disturbances, which can be quite severe. Cidofovir is also associated with kidney injury, and in addition, can cause uveitis. Maribavir and letermovir did not carry the toxicity in terms of bone marrow suppression and kidney injury, but maribavir is associated with dysgeusia, which is an altered state of taste. And both of these drugs also have some drug interactions that are important in the post-transplant setting. As an example, maribavir increases the tacrolimus area under the curve. And when letermovir and cyclosporin are used together, cyclosporin increases the exposure of both, and letermovir decreases voriconazole exposure.

Valganciclovir is the antiviral most commonly used for CMV prevention. In this setting, the recommended dose is 900 mg once a day, which should be adjusted for the renal function. And this is currently considered the preferred regimen for prophylaxis. For patients who have oral intolerance, IV ganciclovir can be used instead. And with both of these drugs, myelotoxicity is common. The duration of prophylaxis will depend on the donor and recipient serostatus as well as the type of organ transplant. And depending on these factors, it can last from 3 all the way up to 12 months.

Now, I want to take your attention to this study that looked at letermovir versus valganciclovir in high-risk adult kidney transplant recipients. This study enrolled 601 patients who were randomized to receive either letermovir or valganciclovir for 28 weeks after kidney transplantation. After these 28 weeks, these patients were followed up to 52 weeks post transplant, and the primary outcome was CMV disease. What this study showed was that letermovir was non-inferior to ganciclovir in the prevention of CMV disease through week 52.

But in addition to that, it's very striking to see the differences in the toxicity observed. You can see here that leukopenia and neutropenia were significantly less common with letermovir as compared to valganciclovir. And in a composite outcome of leukopenia or neutropenia, this difference is even more striking.

So this trial was the trial that led to the approval of letermovir for CMV prevention by the FDA and the EMA, and letermovir currently holds this indication for high-risk kidney transplant recipients. Letermovir, therefore, is currently an alternative to valganciclovir for prophylaxis in CMV donor-positive, recipient-negative kidney transplant recipients, especially in patients with leukopenia and neutropenia. And due to emerging data, letermovir can now be considered for prophylaxis in organ transplant recipients experiencing leukopenia and neutropenia due to valganciclovir. It's important to remember that letermovir is not recommended for preemptive therapy due to the lack of efficacy data and emergency of resistance.

In terms of CMV treatment, the standard treatment is still with oral valganciclovir or IV ganciclovir, with IV ganciclovir being reserved for those situations in which there is disease that is either site or life threatening with a very high viral load or questionable GI absorption. Patients being treated for CMV should undergo weekly monitoring of CMV PCR, serum creatinine, and complete blood count. It's important that weekly CMV PCR is performed using the same sample and the same assay to allow you to interpret changes in DNAemia. Serum creatinine will make you be able to decide if dose adjustments are needed, and the complete blood count is necessary to address toxicity. The duration of therapy should be individualized, but for a minimum of 2 weeks and until resolution of clinical symptoms and virological clearance below a predefined threshold or undetectable for one or two weekly samples.

Neutropenia is a common side effect after solid organ transplant, even in the absence of CMV treatment. But if neutropenia occurs while you're treating CMV, these are some management strategies. You can decrease or stop mycophenolate. You can stop trimethoprim sulfamethoxazole. You should look at the renal function and see if any dose adjustment for renal function is needed. But remember that ganciclovir and valganciclovir doses should not be adjusted for leukopenia and neutropenia, only for renal function. Leukocytes and neutrophils can be supported with growth stimulating factors. And if these measures are not sufficient, ganciclovir and valganciclovir can be switched to foscarnet or maribavir, again remembering that letermovir is not recommended for treatment because it has a low barrier for development of resistance.

CMV recurrence can occur after both preemptive therapy or treatment of disease. There are some factors that are associated with recurrence, and those include a low absolute lymphocyte count at the end of treatment, and absence of CMV-specific cellular-mediated immunity. Secondary prophylaxis can be considered in high-risk situations, such as high immunosuppression, a low absolute lymphocyte count, low CMV-specific cellular-mediated immunity, repeated recurrences, and an inability to monitor patients for CMV replication. The best antiviral and duration to use in this situation are not entirely defined. But usually, if doing secondary prophylaxis, it's done for a period of about 8 to 12 weeks.

I'll now move on to Dr. Saullo to talk about refractory and resistant CMV.

Dr. Saullo:
Hi. My name is Jennifer Saullo. I'm a Transplant Infectious Disease provider at Duke University Medical Center. And I want to thank the organizers and Dr. Sylveira for the opportunity to talk with you on this important topic of resistant and refractory CMV.

Refractory and resistant CMV is generally uncommon; however, instances of refractory and resistant disease are increasingly recognized, particularly as more potent immunosuppressive therapies are used for induction and rejection management, alongside increased durations of antiviral exposure. The presence of resistant and refractory infection is concerning due to the significant morbidity and mortality associated with this. This includes the risk for therapy-related toxicities, which we've touched upon, including neutropenia with agents like ganciclovir and valganciclovir, as well as acute kidney injury and metabolic disarray with therapy such as foscarnet, and less commonly, cidofovir.

Multiple risks have been associated with the development of refractory or resistant CMV infection. These include those associated with antiviral therapy, such as improper dosing or exposure or prolonged exposure. Perhaps best illustrated by valganciclovir and ganciclovir is this issue of improper dosing and exposure, when providers often will reduce the dose in the setting of cytopenias, when that's not felt to be an appropriate response to that issue, or in patients with end-stage renal disease on dialysis, or with variable and fluctuating disease of renal dysfunction where dosing may not reach the target therapies that we would like to apply. Other patient-related factors that increase the risk for refractory and resistant CMV infection include the high-risk serostatus, aka the CMV mismatch recipient. We also know that thoracic organ transplant recipients and other specific solid organ transplant patients may be at increased risk, oftentimes due to the higher level of immune suppression applied. And there are also specific genetic polymorphisms that occur in genes involved in CMV viral immunity and control that have been associated with resistant and refractory as well as invasive disease. There are also infection-related variables. Patients with high CMV viral loads, a theme we'll touch upon throughout this talk, as well as the evidence of severe end-organ and tissue invasive disease.

And then finally, we come back to this issue of the net state of immune suppression, and this is controlled by a multitude of variables, including the patient's past and current immune suppressive therapy, integrity of mucosal barriers, cytopenias, underlying comorbidities, and metabolic conditions such as diabetes. All of these lead to impact the net state of immune suppression.

Standardized criteria and definitions have recently been updated in 2024 by the CMV Definitions Working Group of the Transplant Associated Virus Infections Forum. But as with all definitions, there are some limitations in clinical judgment, and focusing on the patient in front of you are paramount. The revised definitions in 2024 consolidated two categories of refractory and probable refractory CMV infection and disease into one category. Refractory CMV is defined as CMV viremia that increases more than a log or persist and does not decline by a log after 2 weeks of appropriately dosed antiviral therapy. And refractory CMV or end-organ disease is worsening in signs or symptoms or progression to end-organ disease in patients that previously did not have that, or a lack of improvement after at least 2 weeks of appropriately dosed antiviral therapy.

There are also important definitions about resistance. And when thinking about resistance, I think it's notable to state that not all treatment refractory patients are attributable to resistance. And CMV resistance is defined as a genetic alteration affecting the in vitro susceptibility and/or clinical response to therapy. And genotypic testing has traditionally been done, most notably by Sanger sequencing, and ideally when submitting a sample, we like the viral load to be above 1000 IU/mL, or 3 logs.

It's also important to remember that certain CMV end-organ disease, such as retinitis or GI invasive disease, are not always associated

with measurable viral loads in either the plasma or whole blood. And in these cases, the virus replicating in these sanctuary sites may need to be ascertained to submit for resistance testing. We define resistant CMV infection, as best illustrated in the figure to the right, which is refractory CMV infection, which we've defined already in that you've initiated antiviral therapy and you've yet to see an appropriate drop in your CMV PCR log, despite 2 weeks of appropriate therapy, with documented resistance to one or more antiviral therapies, as designated by viral resistance testing.

And so we have a question for you. When it comes to treating resistant and refractory CMV in patients with solid organ transplants, which of the following do you find most challenging?

When considering resistance, I think it's really important to focus in on the site of action of these antiviral therapies, ganciclovir, valganciclovir, cidofovir, and foscarnet all target the UL54 polymerase, whereas maribavir focuses on the UL97 kinase, and letermovir acts at a site distal to these therapies inhibiting the viral terminase complex. Ganciclovir and valganciclovir are unique in that they require phosphorylation by the viral pUL97 kinase in order for activation, and this is a common site of resistance.

When thinking about CMV resistance, it's important to mention some terms, the first of which is EC50. EC50 stands for the effective concentration of 50%, that is the half maximal effective concentration. And it's the concentration of the antiviral drug that's required to inhibit CMV growth by 50%. Degree of resistance is typically reported as the fold change in EC50 from the wild-type. The higher the fold change, the greater the degree of resistance, and the lower the likelihood that resistance can be overcome by methods such as increasing the dose of the antiviral. We typically connote EC50 is greater than 5 as high level, and those below 5 as low level.

When thinking about therapies such as ganciclovir, valganciclovir, foscarnet, and cidofovir, we typically utilize ganciclovir and valganciclovir up front. And most commonly, the resistance that initially emerges is with UL97, and with longer courses of therapy we can see resistance at the UL54 gene emerge. This is quite important, because UL54 mutations can be associated with cross resistant to multiple of these antiviral therapies. With maribavir, the mutations associated with resistance typically affect the gene UL97. It's also important to note that preexposure to agents such as ganciclovir can confer resistant mutations at C480F and F342Y, which can result in maribavir resistance. And finally, letermovir resistance typically is associated with the UL56 gene. And as we've stated before, there's a low genetic barrier for resistance with this therapy.

I think when talking about treatment strategies for resistant and refractory CMV, it's important to note that there is no clear-cut best treatment option when dealing with these patients. Treatment is often defined by the clinical scenarios such as disease severity and the presence of other underlying organ disease, such as renal dysfunction or bone marrow suppression, as well as the toxicities associated with these therapies. Many of these therapies have been available since the early 1990s with very few newer agents added to our armamentarium, one of which is maribavir, which we will talk about in just a moment. Therapies that are unique, such as adoptive T cell therapy have had success in other patient populations, such as hematopoietic cell transplantation and some early success in the solid organ transplant population, but are outside the scope of this talk today. In addition, supplemental therapies with IVIG and CMV-directed immune globulin have also been applied in patients with refractory and resistant CMV, particularly in patients with hypogammaglobulinemia, with good success. Letermovir is one of the newer agents added to our antiviral armamentarium, and as mentioned previously, is FDA approved only for prevention and is not utilized up front for treatment, given its lower genetic barrier for resistance and the lack of evidence-based data to support its use in treatment. And then modifications and immune suppression can also be important. For example, the utilization of mTOR inhibitors, such as agents like everolimus and sirolimus are sometimes applied and have antiviral activity against CMV and have been used with success in certain scenarios. And then finally, in cases of refractory and resistant disease, combination therapy has been employed, although I would caution that the utilization of combination therapies such as ganciclovir and maribavir can be associated with antagonistic effects and is generally avoided.

I'd like to talk a little bit more about maribavir, which is one of the newer agents for the treatment of CMV. Maribavir is a benzimidazole riboside, and has a multimodal mechanism of action, which we alluded to in the prior slides. It's FDA approved for adults and children over 12 years of age, weighing greater than 35 kg, with refractory or resistant CMV. It is very highly oral bioavailable, and is available only in the oral formulation with a dose of 400 mg twice a day. And as previously mentioned, it has a very favorable toxicity profile. Importantly, it is metabolized by the cytochrome P450 isoenzyme system. So this is an important consideration in our transplant patients where polypharmacy is often utilized. And then other relevant holes with this therapy include its lack of good CNS and ocular penetration, as well as a lack of activity against viruses such as HSV and VZV.

I'd like to take a little bit of time and talk about the phase 3 trial, the SOLSTICE trial, which resulted in the critical approval for this drug by the FDA for use in refractory and resistant CMV. The key eligibility requirements for patients are listed here. We've mentioned several of these, but I think ones to note as well, is that they require that these patients have two consecutive CMV plasma DNA values greater than 910 and that they adequately adhere to therapy. Patients were then randomized to one of two groups in a 2:1 open-label fashion, either maribavir at a dose of 400 mg twice a day for 8 weeks, or investigator-assigned therapy for 8 weeks, which could include

valganciclovir, ganciclovir, foscarnet, or, less commonly said, cidofovir, and combination therapy was allowed. Notably, the randomization was done based on transplant type as well as the level of CMV DNAemia. The patients that were in investigator-assigned therapy were allowed to come into a rescue arm and receive maribavir at the doses stated, and then the patients were followed for 12 weeks after treatment.

Results from the trial that I think are worth mentioning include the patient characteristics here described in Table 1. While both solid organ and hematopoietic cell transplant patients were evaluated, the lion's share of patients were solid organ transplant patients, most notably kidney and lung with very few hearts and other organ groups included. Moreover, the majority of the patients had a baseline level of viremia that was below 9000, what we would generally consider to be low-level viremia in this clinical trial. At 8 weeks, patients treated with maribavir achieved a higher rate of CMV clearance in the blood than those receiving investigator-assigned therapy. These results were consistent across the transplant types, and we know that the time to CMV clearance was earlier in patients who received maribavir and then in those that received investigator-assigned therapy.

For the secondary endpoint, the composite of confirmed CMV viremia clearance and symptom control at the end of the study-assigned treatment maintained through we 16, maribavir was also superior to investigator-assigned therapy, although you can see that patients with initial clearance of viremia did have relapse as we moved further along off of therapy. This was seen in both the maribavir arm and in the investigator-assigned therapeutic group.

Importantly, the clinical trial showed what we felt to be true with maribavir, which was that it was generally well tolerated. When looking at any treatment-emergent adverse events, we saw them in both groups, but less patients in the maribavir arm discontinued therapy due to treatment-emergent adverse events. Moreover, when we think about side effects most commonly associated with ganciclovir and valganciclovir, such as leukopenia and neutropenia, the side effect was far less common in the maribavir treatment arm.

When thinking about toxicities that we are concerned about with foscarnet, such as acute kidney injury and electrolyte disarray, again, the maribavir treatment arm had far less side effects in this context. And the primary side effect which was seen in the maribavir arm was dysgeusia, demonstrated in 37% of the patients receiving maribavir. There were some other key takeaways from this. Later detailed genotypic resistance analysis showed that in roughly 1/4 of patients treated with maribavir, genotypic resistance did emerge. The majority of this was in patients who were non-responders, including those patients that initially showed clearance with ultimate rebound, suggesting that rebound in CMV DNAemia while patients are receiving maribavir strongly suggests the evolution of drug resistance. And I've listed here some of the baseline maribavir resistance testing that was seen that may have been connoted by their previous exposure to ganciclovir is some of the primary mutations in UL97 that emerged on therapy. And these mutations emerged roughly a medium of 56 days after maribavir was initiated.

The other point to make on this slide is that we feel that resistance in these patients typically would occur in patients with high levels of viral replication, yet the majority of the patients in the phase 3 trial had a baseline value of CMV that was above 9000. In the patients included in the trial that had viral loads above 50,000 only 30% of those patients responded to maribavir therapy. And so putting it all together, what is the suggested empiric approach to manage patients with refractory or resistant CMV infection that's developing on valganciclovir? The first is to ask yourself some clinical questions. How sick is the patient? Do they have evidence of end-organ disease? And think about how we're dosing these patients, are there any concerns about the dose? And we've talked about the issues and concerns about achieving target levels in patients with variable renal dysfunction or on dialysis. Or are there other bioavailability concerns, such as diarrhea and the like? And then there's always the question that comes to mind of patient compliance, which we should always confirm with our patients.

When we are concerned for resistant and refractory infection, the action items include reducing or modifying immunosuppressive therapy as we are able, and submitting genotypic resistance testing in cases where we are concerned. We also want to assess for the presence of co-infections, as we know that these can drive CMV infections. In scenarios where we identify that there's a low viral load, and what that level is, is difficult to say, but many would connote about a viral load less than 50,000 IU/mL, one can consider several options. One, in patients on valganciclovir, you could increase the dose if you're thinking about potentially resistance mutations in UL97 that may confer lower levels of resistance, or changing those patients to IV ganciclovir. Or these are the scenarios where we might consider the utilization of maribavir or foscarnet therapy.

However, in patients with high viral load, where there might be concerns about impaired absorption, such that oral maribavir may not be a good option, or that we may have infection in these sanctuary sites, such as the CNS or in the eye, foscarnet is typically the preferred therapy. And in certain cases, you may consider transitioning to maribavir once the viral DNAemia is optimized and the patient is in better clinical control.

So in conclusion, the management of resistant and refractory CMV is tough, and it's largely based on expert opinion, with the lack of

really good randomized controlled trials to guide our therapy. And there's multiple unanswered questions that we need to optimize outcomes, the first of which is the duration and which antiviral therapies we should be utilizing. The other is whether or not we need to utilize secondary antiviral prevention to prevent recurrent CMV. We need to learn more about these novel therapeutics, such as adoptive T cell therapy and other pipeline therapies. We also need to learn how best to optimize our immune suppression with the use of therapies that we mentioned, such as sirolimus and everolimus, both examples of mTOR inhibitors. And then finally, we need to understand how best to apply CMV-specific cell-mediated immunity and other markers of immune reconstitution, such as absolute lymphocyte count to assist us in delineating therapy duration.

Dr. Silveira:
So now we have a few cases that hopefully will solidify some of the concepts that we discussed today. The first case is on CMV prevention after kidney transplantation. This is a 65-year-old female who underwent disease donor kidney transplant for diabetic nephropathy. She received thymoglobulin induction and her CMV serostatus is donor-positive, recipient-negative. Her immunosuppression is with tacrolimus, mycophenolate, and prednisone. So this patient was started on valganciclovir 900 mg daily, with a planned duration of 6 months, considering her CMV serostatus. And 6 weeks after transplant, her white blood cell count was 1.8, her ANC was 1.1. And in response to that, her mycophenolate dose was decreased by half. But despite this change, her numbers worsened, and 1 week later, her white blood cell count was 1.6 and her ANC was 0.9. Her trimethoprim sulfamethoxazole prophylaxis was held, and the MMF was stopped in an attempt to improve her neutrophil count.

So what are your recommendations to approach this scenario that is quite common?

Dr. Saullo:
Yes, it is quite common, and it is quite difficult oftentimes to manage. And I think there are a couple options. I think one, if needing to stick with valganciclovir, it's important to emphasize to the providers to not dose reduce these patients based on cytopenias alone, that we would only dose reduce that patient if there were modifications necessary for changes in renal function. One of the ways we could continue the valganciclovir would be to attempt to support her with GCSF. Although that can be tricky. My favorite approach would be to consider changing this patient over to letermovir, an agent we know that has a very favorable adverse effect profile and lacks the cytopenic side effects such as valganciclovir. And so switching this patient to a letermovir-based therapy and utilizing this as our primary prophylaxis would be my preference.

Dr. Silveira:
Yeah, I think this is the perfect example of a patient who really would benefit from letermovir. And this is what we did for this patient. So we stopped valganciclovir and changed her prophylaxis to letermovir 480 mg a day. And with that, her counts improved. Her white blood cell count increased to 2.8, the ANC to 1.9. And once we saw that those counts were stable, we were able to resume her trimethoprim sulfamethoxazole prophylaxis and her mycophenolate, and the white blood cell count and the ANC remained normal while she stayed on letermovir prophylaxis through the initial 6 months of transplant. So she was able to complete her planned prophylaxis post transplant.

Dr. Saullo:
A second case. This is a case of resistant CMV that was seen in a kidney transplant patient. So this was a 60-year-old man with hypertension, diabetes, and end-stage renal disease. He underwent a disease donor kidney transplant, and he was high-risk CMV sero status, i.e., CMV seropositive donor was transplanted into a CMV seronegative recipient. His induction immune suppressive therapy was methylprednisolone, and his maintenance immune suppression consisted of prednisone, tacrolimus, and mycophenolate. We utilized universal prophylaxis with valganciclovir with the plan to use this for 6 months, and the patient was placed on pneumocystis prophylaxis with sulfamethoxazole trimethoprim. Unfortunately, he had multiple early post-transplant complications. He had delayed allograft function and had to return to dialysis on post-transplant Day 1. Thereafter, the team initiated thymoglobulin, and he was given four total doses, but continued to have allograft dysfunction with fluctuating creatinine in the ensuing months after transplantation, and had a biopsy that did not show overt evidence of rejection. Given concerns for calcineurin toxicity, he was transitioned from tacrolimus to belatacept.

And so I'd like to show here the course of therapy and sort of where we were with this patient. So as I mentioned, we started the patient initially on valganciclovir prophylaxis. And as you alluded to, because of his varying renal dysfunction in the post-transplant period and some concomitant leukopenia, he underwent multiple dose adjustments where there was concern that he may not be receiving a dose that target him in the range that we would like for him to – you know, the effective concentrations that we'd like for him to receive. And right around day 50, we began to see that his CMV viral load, which is demonstrated here on the Y axis, began to rise. At that point, the team decreased his mycophenolate, and this is when we did decrease the tacrolimus, and they introduced the belatacept, and the patient was transitioned from prophylactic dose valganciclovir to aggressive induction valganciclovir. And initially with good response.

As you can see in the graph here, his viral load declined and became undetected. But unfortunately, despite, you know, really holding to aggressive dosing, over time, the patient's viral load began to rise multiple logs. At that point, the team, you know, confirmed compliance. They reduced his immune suppression, they held his belatacept, they held the MMF, and they then sent his testing off for genotypic resistance, and he demonstrated one of the canonical UL97 resistance mutations, L595S. So we're left here with a patient with, you know, rising viremia, despite appropriately dosed valganciclovir. And I guess my question to you at this point is, what treatment options would you be considering at this time?

Dr. Silveira:
Yeah, so this is challenging, as all these cases of resistant CMV. At this point, you already know your mutation, so as you discussed, there are some mutations that are associated with a high EC50. So in this particular case, I don't think that giving a high dose of ganciclovir or valganciclovir would be helpful, because this is a mutation associated with high level of resistance. So the options would really be maribavir and foscarnet. And there are few things to consider with both of them. With maribavir, you know, your DNAemia is at the high level. So it's one thing to keep in mind, but at the same time, this is a patient who had a kidney transplant recently and is experiencing, you know, some degree of kidney injury, so I would be very reluctant to use foscarnet, although it would be an option. My preference in this situation would be to use maribavir.

Dr. Saullo:
And that exactly is the conversation, you know, that was had in this patient with, you know, in the early period after a renal allograft is already showing signs of dysfunction, the team was very hesitant to put the patient on foscarnet, and so the patient was put on maribavir. And he tolerated it well. He had some odd dysgeusia, but otherwise did well. And initially we saw good response with a multiple log decrease in his viral load. But unfortunately, despite confirming compliance and the patient otherwise remaining clinically stable, we then began to see an increase in the viral load. And so a repeat genotype was performed. It demonstrated the prior, already known UL, the canonical UL97 mutation, as well as the T409M mutation, which confers high level resistance to maribavir. And with that, and the clinical concern for maribavir resistance, the patient was transitioned, ultimately, to foscarnet.

And I think, you know, just kind of stepping back here, I think the real-world experienced with maribavir would further support the findings of the clinical trial, which is that there is a meaningful rate of maribavir resistance, particularly in patients with high viral loads. And this patient, at the start of therapy, had a viral load that was above 4.5 log. And so when you're seeing an initial decline followed by a viral load rebound, you really need to be thinking about, you know, maribavir resistance in these patients.

So this patient was ultimately started on foscarnet. He did have some worsening acute-on-chronic kidney disease, but generally speaking, he tolerated it okay. He had some genital irritation, some pain and discomfort at his urethral meatus, which resolved. And ultimately we were able to get the patient's DNAemia under control and to the level of undetected. And we're left with the clinical question at this point of what to do now.

Yes, you know, I didn't mention, but in this patient, the absolute lymphocyte count, you know, remained in the 300 to 500 range. And the team was obviously very concerned about his renal function and the potential need for him to go back on foscarnet therapy. And it does, it comes to this question of, you know, when should one stop CMV-directed therapy? And ideally, you should have evidence of virologic clearance and with at least 1 to 2 weeks of undetected or detected but below the limit of quantification value on the assay. And ideally, have respiration of CMV immunity, which in this case, in our patient, was really difficult to demonstrate. There are multiple ways to consider doing that. One is utilization of some of the differing CMV-specific cell-mediated immunity assays also looking at the absolute lymphocyte count. But we know that early cessation runs the risk of clinical as well as virologic recurrence. And what to do here, you know, the evidence-based literature is limited.

And so in this case, we did exactly as you mentioned, is that we put this patient on secondary letermovir. We were fortunate enough to get insurance approval for that, and the patient actually tolerated that therapy quite well. When utilizing letermovir for secondary prophylaxis, we all realize that while it's not FDA approved for this indication, it's really approved for primary prophylaxis in the hematopoietic cell and solid organ transplant population. There is data, primarily based on case reports in single-center retrospective studies, that would support the use of letermovir for secondary prophylaxis. And in general, that data has mixed results, but overall, the therapy has been well tolerated. There have been issues of breakthrough infections and resistance emergence, and we've mentioned multiple times in this talk the low genetic barrier for resistance with letermovir. And I think the literature is difficult to evaluate, because there are a multitude of factors that can contribute to the success or failure of therapy. It includes, again, that net state of immune suppression, ensuring that the CMV DNAemia is undetected at the time of transitioning, so we don't want to be utilizing letermovir when there's, you know, particularly high level, but really any level of DNAemia in this particular case. As well as considering prior antiviral exposure, and has this patient seen letermovir in the past? And again, making sure that we're utilizing the correct doses of letermovir, keeping in mind the concomitant therapies that the patient's on, most notably, whether the patient's receiving cyclosporine or tacrolimus,

which can result in needs for dose adjustments.

And so I guess the question for the collective is, now that you've completed this activity, what do you continue to find challenging when managing CMV in patients with solid organ transplants?

That is all the time we have today. Thank you, Dr. Silveira, for your time today, and thank you to all of our learners for joining us. Please don't forget to take the posttest and complete the evaluation to receive your credit. And thank you.

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