Transcript Details
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Managing Refractory Cytomegalovirus Post-Solid Organ Transplant

Announcer:
Welcome to ReachMD. This medical industry feature, titled “Managing Refractory Cytomegalovirus Post-Solid Organ Transplant,” is sponsored by Takeda.

Here’s your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I’m your host, Dr. Jennifer Caudle. Joining me to discuss the management of cytomegalovirus, or CMV, after solid organ transplant is Dr. Suphamai Bunnapradist. He’s a Professor of Medicine in the Division of Nephrology at the UCLA Medical Center. Dr. Bunnapradist, it’s great having you here today.

Dr. Bunnapradist:
Thank you for having me, Dr. Caudle!

Question 1:

Dr. Caudle:
So why don’t we start with a little bit of background on CMV infection after solid organ transplant. Dr. Bunnapradist, what can you tell us?

Dr. Bunnapradist:
Well, the great news is according to the United Network of Organ Sharing.[1] Nearly 43,000 solid organ transplants, or SOT, were performed in the United States in 2022 alone.

But patients can develop post-transplant CMV, one of the leading cause of morbidity and mortality after solid organ transplant.[2,3]

These infections can be refractory, meaning there’s a persistent viral load at least after two weeks of adequate antiviral treatment,[4,5] or resistant, which is a term meaning that there’s a refractory and also an altered viral genetic sequence that decreases susceptibility to one or more of the antiviral treatments.[4,5] Fortunately, tremendous progress has been made since the first kidney transplant between identical twins in 1954, 70 years ago, including advances in immunosuppression, testing, and treatment of common complications.[6,7] But despite the current available options for prevention preventing and treating CMV infections, I’ve still seen SOT recipients unable to clear the virus.

Question 2:

Dr. Caudle:
Thanks for providing that background, Dr. Bunnapradist. And with that in mind, let’s examine refractory CMV after SOT through the lens of a hypothetical patient case. What details do you have to share with us?

Dr. Bunnapradist:
So, we have a 57-year-old male who received a renal transplant due to adult polycystic kidney disease. The donor had died from drug intoxication. This patient’s CMV serostatus was negative, but the donor was positive, meaning that this is a high risk CMV transplant patient. So for CMV prophylaxis, he was treated with a 3-month course of valganciclovir.

At month 2, he was treated for acute cellular rejection and his immunosuppressive regimen was adjusted to tacrolimus 3 mg and mycophenolate 360 mg, both dosed twice daily. But at month 4, one month after prophylaxis was done, he was admitted to the hospital with fever, malaise, worsening leukopenia, and thrombocytopenia, and his CMV viral load was 44,700 IUs per milliliter confirmed by the PCR.

At this point, he received IV ganciclovir, and his immunosuppressive regimen was reduced. PCR testing was repeated at 7 days and 15 days, and his viral load had increased to 141,500 and 198,000 IUs per milliliter, respectively. His creatinine level had also increased from 0.74 milligrams per deciliter at admission to 1.3 milligrams per deciliter.

Question 3:

Dr. Caudle:
So then what treatment options might we consider for this patient?

Dr. Bunnapradist:
We could try several things. We could try to treat him with higher dose of ganciclovir, we could use cidofovir, or foscarnet IV, but now we do have an alternative option called LIVTENCITY, or maribavir. LIVTENCITY is indicated for the treatment of adults and pediatric patients 12 years of age and older weighing at least 35 kg with post-transplant CMV infection or disease that is refractory to the treatment —with or without genotypic resistance, and the resistance can be to either ganciclovir, valganciclovir, cidofovir, or foscarnet.[8]

And I would like to note that lab testing to confirm genotypic resistance to the current treatment is not needed before switching a patient to LIVTENCITY. If a patient has CMV that is not responding to the current treatment and is considered refractory, that is 2 weeks and no response, then the patient may be a candidate for LIVTENCITY.[8]

Dr. Caudle:
Thanks, Dr. Bunnapradist. Now, let's take a moment to review some Important Safety Information for LIVTENCITY.

Announcer:
IMPORTANT SAFETY INFORMATION
Risk of Reduced Antiviral Activity When Co-administered with Ganciclovir and Valganciclovir
LIVTENCITY may antagonize the antiviral activity of ganciclovir and valganciclovir by inhibiting human CMV pUL97 kinase, which is required for activation/phosphorylation of ganciclovir and valganciclovir. Coadministration of LIVTENCITY with ganciclovir or valganciclovir is not recommended.

Virologic Failure During Treatment and Relapse Post-Treatment

Virologic failure due to resistance can occur during and after treatment with LIVTENCITY. Virologic relapse during the posttreatment period usually occurred within 4-8 weeks after treatment discontinuation. Some maribavir pUL97 resistance-associated substitutions confer cross-resistance to ganciclovir and valganciclovir. Monitor CMV DNA levels and check for maribavir resistance if the patient is not responding to treatment or relapses.

Question 4:

Dr. Caudle:
So, Dr. Bunnapradist, before we check back in with our patient, let's examine the clinical trial for LIVTENCITY. How was the study designed, and what were the key endpoints?

Dr. Bunnapradist:
Right. So, the SOLSTICE is the trial that led to the FDA approval of the drug. SOLSTICE is a phase 3, multicenter, randomized, open-label, active-controlled superiority trial in patients who received either solid organ transplant or hematopoietic cell transplant. It was designed to evaluate the efficacy and safety of LIVTENCITY versus investigator-assigned treatments, or IATs for short, and investigator-assigned treatment include one or two conventional CMV antiviral drug. These include ganciclovir, valganciclovir, foscarnet, or cidofovir.[8,9]

The primary endpoint was confirmed CMV DNA level below LLOQ, or lowest level of quantification, meaning below 137 IUs per milliliter in two consecutive samples tested at least 5 days apart, at the end of week 8.[8,9] The key secondary endpoint was CMV DNA level below LLOQ and CMV infection symptom control at week 8, with maintenance through week 16.[8,9]

Now I think it's important to note that this clinical trial design had some limitations. Having a clear objective, inclusion criteria, and measurement of treatment time by necessity may not always reflect true clinical practice. Some study limitations included this is an

open-label study, which meant that blinding wasn't feasible, and this is due to individualized IAT drug selection in many of them and the dosing adjustments are different, with different administration compared to LIVTENCITY. Also, the clinical trial enrolled only adults 18 years and older. The study, also, wasn't powered enough to detect differences between the treatment arms in patient subgroups, and patients were not stratified by refractory or resistant CMV upon randomization. Lastly, study-specified treatment duration may have required patients with residual CMV at the end of week 8 to receive alternative treatment, so they were not classified as non-responders.[8,9]

As I mentioned a few moments ago, the study only included patients who were 18 and older, but LIVTENCITY can also be used in pediatric patients who are at least 12 years old and who weigh 35 kg or more.

This is based on a couple different factors, including evidence from controlled studies of LIVTENCITY in adults and population pharmacokinetic modeling and simulation that demonstrated that age and body weight had no clinically meaningful effect on plasma exposures of LIVTENCITY. Now in terms of LIVTENCITY's exposure, it is expected to be similar across all patient populations.

And since the course of the disease is also similar among these two patient groups, this allow us to extrapolate the data in adult to pediatric population. Also important to keep in mind that LIVTENCITY's safety and effectiveness have not been established in children younger than 12.[8]

And now, I would like to review some baseline characteristics for the SOT patients involved. The trial arms were balanced by multiple adult patient parameters and included several types of transplant.

Among 40% of patients had undergone hematopoietic cell transplant, while the other 60% received SOT. SOT recipients were mostly recipients of a kidney, lung, or heart, though there were a number of patients with liver, pancreas, intestine, or multiple organ transplants.[8]

So a range of CMV DNA levels at baseline were seen, though only 6 percent of patients in each arm had high levels, more than 91,000 IUs. Intermediate CMV DNA levels, defined by those CMV DNA measured between 9,100 and 91,000 IUs per milliliters, were seen in 29 percent of patients in the LIVTENCITY arm and 21 percent of patients in the IAT arm. And it's important to note that 65 percent of the LIVTENCITY group and 73 percent of the IAT group had CMV DNA levels below 9,100 IUs per milliliter.

Symptomatic CMV infection was seen at baseline in 9 percent of patients in the LIVTENCITY arm and 7 percent in the IAT arm. Among the symptomatic patients, 57 percent in the LIVTENCITY arm had tissue invasive disease, while only one of the symptomatic patients, or 13 percent, had tissue invasive disease in the IAT arm at baseline.

And finally, the mean age of trial subjects were 53 years, and most subjects were male, white, and not Hispanic or Latino, with similar distributions across the two treatment arms.[8]

Question 5:

Dr. Caudle:
So, Dr. Bunnapradist, now that we know how the SOLSTICE study was designed, can you walk us through the key findings?

Dr. Bunnapradist:
Of course! So as for the primary endpoint, a significantly higher proportion of patients who received maribavir achieved CMV DNA level below lower levels of quantification at week 8 versus IAT. In fact, 56 percent of patients in the LIVTENCITY arm achieved the primary endpoint versus 24 percent in the IAT arm.[8] This demonstrated statistical superiority of maribavir over IAT.[8,9]

Some patients who achieved CMV DNA level less than LLOQ experienced virologic relapse, also known as recurrence, during the follow-up period, which was defined as 4 to 8 weeks after treatment discontinuation.[8]

After the end-of-treatment phase, 50 percent of patients in the LIVTENCITY group and 39 percent of the patients in the IAT group who achieved CMV DNA level below LLOQ experienced virological relapse during follow-up, with most occurring within the 4 weeks of discontinuation—specifically, the median time to relapse was 15 days.[8] However, this is expected; secondary prophylaxis was not recommended during the 12-week follow up period, and this doesn't necessarily reflect what happens in true clinical practice.

Additionally, virological failure due to resistance can occur during or after treatment. Thirty-four percent of patients experienced virological failure on LIVTENCITY versus 36 percent in the IAT arm due to not having, achieving CMV DNA level below LLOQ or have CMV DNA breakthrough.[8]

Question 6:

Dr. Caudle:
And how about the secondary endpoint? What were the results there?

Dr. Bunnapradist:
The secondary endpoint was met as well, and investigators found a significantly higher proportion of patients on LIVTENCITY achieving CMV DNA level below LLOQ and symptom control at 8 week, and they maintained efficacy through week 16.[8] Symptom control was defined as resolution or improvement of tissue-invasive disease or CMV syndrome for symptomatic treatment at baseline or no symptoms in patients who were asymptomatic at baseline. These patients were considered responders.[8]

But in both treatment arms, the percentage of patients achieving the composite endpoint was lower than the primary endpoint due in part to virologic relapse, reflecting the latent nature of CMV infection when the virus may reactivate in periods of ongoing immunosuppression.[9]

Additionally, the response in subgroups related to treatment or disease characteristics were consistent with the response observed in the primary analysis or in the randomized overall population of patients with refractory or resistant CMV.[8,9]

Now virologic resistance to LIVTENCITY was observed during the study follow-up period. In patients with phenotypic resistance to valganciclovir or ganciclovir, DNA sequence analysis of the entire coding regions of pUL97 and pUL27 was performed on paired sequences from 134 LIVTENCITY-treated patients. Treatment-emergent pUL97 resistance-associated substitutions, or RAS, were detected in 58 patients, 47 of them being on-treatment failures, meaning that non-responders to the primary endpoint, whereas 11 were considered relapsers, which is after 8 weeks of the treatment.[8]

And finally, in terms of cross-resistance, pUL97 RAS reduced susceptibility to LIVTENCITY by more than 4.5-fold. Some substitutions in pUL54 conferred cross-resistance to valganciclovir and LIVTENCITY, and those who developed resistance during the trial were still being treated with foscarnet.[8]

Question 7:

Dr. Caudle:
Thanks, Dr. Bunnapradist. And if we go back to our patient case, what steps were taken to treat him, and how did he fare?

Dr. Bunnapradist:
Well, an infectious disease specialist was consulted because of this patient's rising viral load and serum creatinine that I mentioned earlier, and he was initiated on LIVTENCITY 400 milligrams twice a day orally. After 2 weeks, the viral load dropped to 1,669 IUs per milliliter, and after another 2 weeks, down to 1,321 IUs per milliliter, as confirmed by the PCR.

The patient reported dysgeusia but no other adverse events related to treatment. After 6 weeks on treatment , his CMV DNA level had dropped below LLOQ, which is less than 137 IUs per milliliter. And after 8 weeks on treatment, LIVTENCITY was stopped. He was checked monthly by CMV PCR through month 11, and his CMV DNA level remained below LLOQ, with no evidence of CMV reactivation.

Question 8:

Dr. Caudle:
Well, that's encouraging to hear, and thank you for sharing how LIVTENCITY can be used for post-transplant refractory CMV. But I'd like to zero in on something you touched on earlier, which was the adverse events related to LIVTENCITY. So what do we need to know about the safety data and recommended dosing?

Dr. Bunnapradist:
Right. So the SOLSTICE trial showed a lower rate of treatment discontinuation due to adverse events with LIVTENCITY versus IAT.[8]

In the LIVTENCITY arm, 13 percent of patients discontinued due to adverse events, the most common at 1 percent each being taste disturbance that our patients have, diarrhea, nausea, and recurrence of underlying disease.[8] In the IAT arm, the discontinuation rate from adverse events was 32 percent, with the most common being neutropenia at 9 percent and acute kidney injury at 5 percent.[8]

And I would like to note that our patient did experience taste disturbance, and this is consistent with the LIVTENCITY arm of the trial, at 46 percent of the 234 patients experienced dysgeusia. Taste disturbance rarely led to the treatment discontinuation though, and it resolved in 37 percent of patients while on treatment and in 89 percent of patients post-treatment.[8]

And here we can see the adverse events, of any grade, that were reported in >10% of adult patients for LIVTENCITY. Taste

disturbance was the most common adverse event reported in the LIVTENCITY arm. Patients in the LIVTENCITY arm had similar rates of nausea (21%), diarrhea (19%), vomiting (14%), and fatigue (12%).[9]

As for dosing, 400 milligrams—or two 200-milligram tablets twice daily—is recommended for adults and children 12 years and older weighing at least 77 pounds.[8] LIVTENCITY can be taken as whole, dispersed, or crushed tablets by mouth, or as dispersed tablets through the NG or orogastric tube. Please refer to the full prescribing information for more details. Dose adjustments will be needed if it's co-administered with certain anticonvulsants, but no dose adjustment is needed for patients with mild, moderate, or severe renal impairment or mild to moderate hepatic impairment.[8]

Potential drug-drug interactions may also occur with immunosuppressants, antiarrhythmics, and antimycobactoerials.[8] And while the patient in our case wasn't taking any of these concomitant agents, those who are should be monitored for drug levels frequently throughout treatment, especially after initiation and discontinuation so that the medication can be adjusted accordingly.[8]

Question 9:

Dr. Caudle:
Now we've certainly covered a lot today, Dr. Bunnapradist, but before we close, what key takeaways would you like to leave with our audience?

Dr. Bunnapradist:
Yes. Although refractory CMV is a leading cause of morbidity and mortality after SOT,[2,3] LIVTENCITY is an effective treatment option for post-transplant refractory CMV per the data from the SOLSTICE trial that I showed you earlier.[8]

And as was the case for our case patient here, he experienced taste disturbance that resolved post-transplant. Again, this is similar to what was seen in the SOLSTICE trial as taste disturbance resolved in 37 percent of patients while on treatment, and in 89 percent of patients post-treatment.[8,9]

Dr. Caudle:
Well those are some great thoughts to take with us as we come to the end of today's program. I'd like to thank my guest, Dr. Suphamai Bunnapradist, for helping us better understand LIVTENCITY as a treatment option for CMV after SOT. It was great speaking with you today.

Dr. Bunnapradist:
Thank you so much for having me!

Dr. Caudle:
For ReachMD, I'm your host, Dr. Jennifer Caudle. And please stay tuned to hear more Important Safety Information for LIVTENCITY.

Announcer:
Important Safety Information (Continued)

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions.

- The concomitant use of LIVTENCITY and certain drugs may result in potentially significant drug interactions, some of which may lead to reduced therapeutic effect of LIVTENCITY or adverse reactions of concomitant drugs. Consider the potential for drug interactions prior to and during LIVTENCITY therapy; review concomitant medications during LIVTENCITY therapy and monitor for adverse reactions. Refer to the full prescribing information of LIVTENCITY for important drug interactions.
- Maribavir is primarily metabolized by CYP3A4. Drugs that are strong inducers of CYP3A4 are expected to decrease maribavir plasma concentrations and may result in reduced virologic response; therefore, coadministration of LIVTENCITY with these drugs is not recommended, except for selected anticonvulsants.

Use with Immunosuppressant Drugs

LIVTENCITY has the potential to increase the drug concentrations of immunosuppressant drugs that are CYP3A and/or P-gp substrates where minimal concentration changes may lead to serious adverse events (including tacrolimus, cyclosporine, sirolimus and everolimus). Frequently monitor immunosuppressant drug levels throughout treatment with LIVTENCITY, especially following initiation and after discontinuation of LIVTENCITY and adjust immunosuppressant dose, as needed.

Adverse Reactions

- The most common adverse events (all grades,> 10 percent) in subjects treated with LIVTENCITY were taste disturbance, nausea, diarrhea, vomiting, and fatigue.

Announcer:
This program was sponsored by Takeda. If you missed any part of this discussion, or to find others in this series, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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