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TRANSCRIPT - GR 12 16 22 "Treatment of Resistant and Refractory CMV - Where do we Stand in 2022?" Daniel Kaul, MD, from University of Michigan Health

UVA Medicine Grand Rounds

- Well welcome everyone. Welcome to those of you who have come to enjoy our Panera here in the Rca. And to those of you who are joining on Zoom today's medicine grand round. So I'm excited to introduce Dr. Daniel
- Cowl call, I believe, actually from the University of Michigan. Dr. Call directs the transplant infectious disease service at the University of Michigan, which provides inpatient and outpatient consultation for patients who have received either a solid organ or a STEM cell transplant.
- He also serves as the infectious Disease Fellowship Program Director His research interests include the epidemiology of opportunistic infections after solid organ transplant and the diagnosis and management of viral and other opportunistic infections following STEM, cell transplant.
- he is the past chair of the United network of organ sharing's, Disease Transmission Advisory Committee and serves as the Education on the Education Committee of the American Society of Transplantation and the Program Directors Committee of the Infectious Z. Society of America.
- He is a wonderfully thoughtful commission, a dedicated educator and mentor, and a talented communicator of complex medicine, both to the public and to the medical community at large. So please welcome Dr. Daniel call.

Daniel Richard Kaul

00:16:59

Thanks so much Sam. Wish I could be there in person and get some panero with you. But I guess we'll just have to do it. virtually so. The title of my talk today is a treatment of resistory resistant refractory, Cmv. Where do we stand in 2,022, and I picked that title because there are some new drugs available. in the last few years which is really exciting for those of us who deal with Cmb infection, and, you know, compromise patients, because even in my entire career, now, and since I've been in medical school there haven't been any new drugs license, and that's getting to be a long time. So it's exciting to have some other options, and so I hope to share some of that information with you.

- Here are my disclosures so I'll definitely provide some background, you know, in general, on side of Megalvirus, and it's epidemiology and kind of the general strategies we use to address

it in both solid organ and STEM cell transplants, and then we'll focus down on resistant and refractory.

- Cmv. And talk about these 2 newer agents. The term of here, which was approved in 2,017, largely for prevention of Cmv. And STEM cell transplant patients and ribbons, which is a drug which had kind of been kicking around for almost 20 years of development but was approved in November of 2,021 for resistant and refractory, Cmv.
- So if we talk about Cmv. In general, you know those of you who came to the room today to get the Panera. you know, if you look to the left and the right of yeah, there's about a 50% chance that the person next to you is is 0 positive for Cmv: the United States. The serial problems about 50 in other countries that may have more crowded conditions, or for other reasons, the 0 prevalence rates can go above 80 90% in adults. And so what that means is that if you're a solid organ transplant recipient, for example, there's about a 50% chance that you're a 0 negative recipient of a 0 positive donor, and that's the highest risk situation which shouldn't Be that surprising, because that means you don't have any immunity. Cmv: and we're putting either one or 2 big wet bags of Cmv into you, and then immunosuppressing you. So the risk of infection is certainly there. again, in countries with higher serial problems. There's higher baseline immunity, and actually the concern or the problem, or the effect of Cmv. Maybe less overall in that population for the STEM cell transplant patients. It's really being recipient positive. That's the issue, because you're not going to get Cmv with the with the STEM cells which are filtered and shouldn't have cmv in them. and so that risk is about 50% of people would be in the higher risk group in that circumstance.
- So we'll start with a few just some definitions. so the term Cmv infection just means any micro biologic evidence of cmv replication. And really technically, the way we measure it. Now, there used to be antigen assays and other things, but pretty much we do quantitative nucleic acid testing usually. Pcr. that gives us a quantitative result of how much Cmv. Is in the the plasma.
- So really what we're measuring is Cm. V. A. DNA Emia. So. whether that's all replication. Competent virus is a different question. We've kind of learned that when you think about Covid right where people can often test positive for months, especially if they're, you know suppressed, and you may just be picking up fragments that Don't really indicate replication. Competent virus. But nonetheless Cmv. Infection just means usually that we can find a positive pcr and symptoms. are often not present in that circumstance. and then Cmv disease. We can divide kind into 2 categories. One is Cmv. Syndrome, which used to just sort of be fever, leukemia, and severe fatigue, often with some mild g symptoms a little bit of nausea, a little bit of diarrhea. And a patient told me it was probably about 1520 years ago, Doc, I feel like every cell in my body is tired, you know. And now, when I ask that to a a patient they used to go. Yep, that's it. That's exactly how I feel. And Dr. Siffrey, who I can see Hi Costy would probably agree with me that the severe fatigue is, you know, by no means like path and mnemonic. It's just fatigue, but it's quite characteristic of Cmv disease, because of the immune perturbations and activation associated with Cmv. Then, and organ disease technically means that you got some biopsy evidence of Cmv. And a tissue so that might occur. For example, hepatitis and a liver transplant recipient. You do a biopsy. You find a whole bunch of virus states on amino acid chemical stating that show, Cmv.
- And then you'd say you had and organ disease. Now, sometimes it's obvious that there's an organ disease without the bip. See somebody with a bunch of ground glass infiltrates with

micronodular disease, with hundreds of thousands of millions. Copies of Cmv. Almost certainly has in their class. M. Almost certainly has Cmp. Pneumonitis, and there you generally wouldn't need a biopsy to make that diagnosis. But those are the kind of the definitions.

- And then what's the spectrum of disease associated with Cmv. So we'll start just by discussing, you know, competent people. So I already told you that half of the half the people in the United States have had. Cmv. But many of them may not even have known it when they got infected. Now it certainly can cause a mono like illness, often with less
- lymph anopathy, and less severe sore throat, but otherwise somewhat indistinguishable for Mono. And so, if somebody actually makes it to an infectious disease. Doctor, with concerns about Mono. I usually include a Cmv. Igm. And that's the only time I can think of where I really ever order a herpes virus igm, because they're notoriously useless and confusing. but sometimes those people are seeing the igm negative and ig positive, although they may have already circ converted to ig in that circumstance. but at least then, if you include that in your kind of mono workup you can have a diagnosis. Sometimes, if the mono testing is negative, and of course, if you look at the burden of Cmv disease in the world, probably most of it is not so much what we face in, you know, surprised people, but congenital Cmv. And there's lots of work to try and reduce that. Of course Cmv. Is one of the torch infections. So it's not really typically reactivation in a woman that causes the problem during pregnancy. But new infection.
- There are some exciting things being worked on, and vaccination, and so forth, to help deal with that.
- The other thing that will occur is Cmv. It's a latent virus, just like all the other herpes viruses, and it can reactivate in situations of stress. So if you go to our one of our icu's at Michigan, and I’m sure it's this, and it's the same in Virginia.
- you would see. and you did. Cm. V. Pcrs quantitative Pcrs and the plasma. You'll find a whole bunch of people who are positive, and while there's been some interest in it, there's no clear evidence that treating those people is helpful. It's often a very low level, positive, and can actually just be confusing, which is often true of any of these, either late or viruses that reactivate when you look with very sensitive testing, you'll find it when there really isn't any
- anything to be done about that positive task. So let's move on to immunosuppress patients. So in solid organ transplants the disease can often begin in the transplanted Oregon. So a lung transplant patient may start with new menitis. A liver transplant patient. This is in the donor. Positive, recipient. Negative circumstance may start with hepatitis. You can get nephritis and kidney transplant patients, and then the disease can kind of disseminate from there. and in HIV infected patients I haven't seen a significant problem with Cmv. And HIV infected patients in a long time. What we used to see a lot in the in the in the nineties. That's at least when I started working with HIV patients as you would get large geographic ulcers in the gi tract. for example, with a lot of pain a little bit different than the kind of more nausea diarrhea that we tend to see in a solid Oregon or STEM cell transplant patients. and retinitis was also very common, and of course that can happen in any group with Cmv. but was particularly common in HIV. Infected patients.
- STEM cell transplant patients again. It's the recipient positive because you're taking away their immunity. They've got Cmv in them, and that's where you get reactivation rather than it coming with the STEM cells, or coming with the Oregon as it does in solid organ transplant.

- In another group worth mentioning is those with inflammatory bio disease where it's not uncommon when they're getting a byipseed of by to their G. I track for some other reason that you'll see just a rare or scattered virus side, and often that actually doesn't require any treatment. It can be tricky to figure out whether that's really the problem or not in that population.
- and no talk with Cmv. Would be complete without mentioning the indirect effects of Cmv. Because when you look at the biology of the of the virus it's quite immunosuppressive. It activates a lot of different parts of the immune system, and creates all kinds of problems. a number of years ago we looked at all our new assistance cases, and in about 1,300 kidney transplants, and half of them followed Cmv infection, or associated with chronic Cmv infection. So sometimes you even think about adding some prophylaxis, not everybody with Cmv. But when you have chronic recurrent infections for things like new assist, and then there are also some transplant specific indirect effects. The most kind of talked about. One is alligraph vascularopathy after cardiac transplant, or where even single episodes of Cmv can increase the risk of developing, essentially a vascular disease. Again, in the in the in the blood vessels, to the to the grafted, heart rocky latest of blitter ands after lung transplant is also associated with Cmv infection. So it while we have ways to control and lots of good drugs that it remains a huge problem in immunosuppress patients and this was a study fairly recently published. Well, 2,017. That was one of these kind of diagnostic code database studies, but it looked at every the entire population in France to try and assess
- with, if there was codes for Cmv. How that affected things like graph rejection, graph failure, mortality, and solid organ transplants and you can see whether it was early disease occurring after 3 months or after 6 months that it was generally associated with all those bad outcomes, including mortality. So there are even a few centers. It's pretty uncommon. But there are a handful of centers that try and sort of 0 sort their transplant recipients. So if you're negative, they try and find a negative organ for you. That, of course, excludes half of the organs, and being on the wait list for a transplant not getting a transplant quickly is certainly associated with bad outcomes, but nonetheless, even with all our strategies, to control Cmp. The burden of disease is still significant. So what are the general strategies to control disease. Most centers do universal prophylaxis. And what that means is that patients at risk for Cmv. Which would be anybody who isn't 0 negative from a 0 negative donor receives some period of time. Usually it's in the 3 to 6 month time, but even as long as a year for higher slung transplants will receive.
- They again cycle of your prophylaxis. The other strategy is preemptive monitoring, and what that means is, you do a Pcr. frequently. You've really got to do it as a as frequent as weeky l in high-risk patients because cmv doubles very quickly. You can see a day and a half or so in high risk patients, and you want to be able to intervene, meaning put them on a drug because they've become serial pop, because they've developed a DNA emia before a disease develops. And you know, this is hard to implement it's actually as I'll show you. It may be a superior strategy long term at least, if you look at Cmv. Disease as the outcome, but it's difficult to implement because somebody's got a check the Cmv every week, and I'm sure it's true in your center. It's certainly true in ours. Many of our patients live far away, but you got to check it.
- Somebody's got to see the result. Somebody's gonna get people on treatment quickly or bad things will happen and this is kind of an interesting study that Was led by a G. Lemay that was

published a couple of years ago. to actually compare the first study. I saw that really compared head to head in a randomized fashion in liver transplant patients high risk liver transplant patients in this case giving Velgan Cyclvere versus monitoring the Cmv Weekly, and then looking at the outcomes of Cmv disease. And what you see is in the antiviral prophylaxis group.

- There was less there was more cmv disease. after this is all after the universal prophylaxis to stop, because rarely does cmv reactivate well on prophylaxis or occur on prophylaxis but the incidence was just about twice as high in the antivir prophylaxis versus those that were on preemptive therapy, even though the people in preemptive therapy, I think it was got 70 or 80 as much Val site, so they almost all needed to be treated because they reactivated but they had much less disease. after the period of monitoring. And why was that? Well, it probably was because they developed good t cell immunity. Many of the patients developed t cell immunity because their Cmp. Naive people these are just different ways to measure t cell responses kind of similar to the quantifier on gold we use for Tb. Where you expose the patients monon nuclear cells to in a Cmb, anigen, or a mix of Cmv. Antigens. And then look at how much interferon they produce, whether it's CD. 4 Lymphocytes, or CD. 8 lymphocytes, and you can see the yellow bars reflect those who received preemptive therapy, and the blue bars are those who received antiviral prophylaxis, and the t cell responses were better because one way to think about Cmv. When we're treating Cmv: what we're really doing is trying to treat it treat disease to try to control it and hope that somebody will develop their own immunity, their own cellular immunity, so they can control it themselves later. Otherwise it just keeps coming back in STEM cell transplants. The burden of disease remains significant as well. So this is a group that isn't getting prophylaxis, and so you can ignore kind of the active treatment groups. But if you look at the 2 these 2 panels here, you can see Placebo in either of these trials 50 to 60% of 0. Positive STEM cell. Transplant recipients will reactivate their Cmv. And treatment can be really difficult, but especially when there's early reactivation, because the drugs that we generally were using. This is before we're using the term of your prophylaxis, which i'll be talking about in detail later cause quite a bit of cytopenias that is, gain, Cyclover or Valc and cycle there, and as a consequence, patients were often admitted to get some fairly toxic drugs like fast carnet, and so the the expense, the time in the hospital and even the mortality associated with early reactivation is quite a significant.
- So let's talk now about Gan cyclvere resistant Cmv. So it happens in solid organ transplants in somewhere in the 2, 3, 4, 5 range. It depends on. When the study was done, and what prophylaxis was being used, and so forth. So it's not terribly common, but when it does occur it's an enormous amount of work and risks to the patient. and if you do a couple of 100 kidney transplants a year that means you may have 4, 5, six-seven cases each year of drug of at least can't cycle various and c. The highest risk group is donor, positive, recipient, negative heart transplants, where you see reported rates of 10 to 15 or so, and we have observed that in our center, as I'll show you later in the past, so the risk factors. The biggest risk factor by far is donor positive recipient negative status. But this is not something you don't get drug resistance. Cmv: because you're exposed to someone with drug resistance. Cmv. You get drug resistance? Cmv: because you're exposed to gans like Levy or valeg and Cyclvere, or some other similar product that then allows resistance to develop, because there's ongoing file replication one that drugs around. And I recall Gus was back around 2,000 or so oral gan

cyclvere, not Valg and cyclover. So Vlog and cyclo, or vowelsite, is merely the Valine ester of gan cyclair, and that increases bio availability Otherwise it's basically the same thing. But there was an oral G encyclopedia that's no longer available which had really poor bio availability and at least the centers in at that time used it pretty widely, and Kenny transplant patients, and it was a great way to make resistant fires, because You're getting very low levels of Gan cycle there some viral reactivation and then resistance could develop.

- So when do you worry about Gans cyclovair resistance? Well, certainly when the risk factors I described or present, and when people aren't getting better so if you're not seeing clinical improvement, if they're Cmv disease or syndrome. Usually people get better. They start to feel better with Cv. Syndrome 4 or 5 days Fevers are better. Stomach feels better, fatigue feels better with Cm. V. Disease. It can take a little bit longer, you know again, depending on what the symptoms are. but usually in 2 to 3 weeks. People are better. So if they're not, you have to at least wonder about resistance. Virologically you should start to see the decrease in the viral load, and 14 to 21 days, just being careful about what your Baseline actually is, because sometimes and with this, you know, if you're having a doubling time of a day and a half, and somebody got checked as an outpaced, and they were 50,000, and they got put on treatment. 4 days later, 150.
- They may be at 4 or 500,000 when they actually started treatment, and then you check them a week later, and they're 200,000, and they actually went down. but it would look like they went up because your baseline 50,000. So you always got to kind of keep that in mind, too, even when these factors are present, though most patients actually don't have resistance, they have another issue the most common one would be that they're immunosuppressions just too high to get the same V under control, and that would often be in STEM cell transplants with graph for so disease. That's been a bit refractory, and they're getting really high doses of
- amino suppression.
- So let's talk just for a second about the mechanisms of resistance. So encyclopedia is a pro drug that requires 3 phosphate groups to be added to it to become active, and that that first phosphate group is added by a the viral kinase it got a viral phosphaterance phase, and so mutations to that, and that is made by the ul 97 viral dream can result in gain cycl of your resistance 100 ninety- but not resistance to Sudo for or fuss carnet to other drugs that we use that act at the level of the viral DNA polymerase and Don't require that phosphorylation. However. if the mutation which up, which rarely occurs prior to all 97, but if they're still getting against cyclvere at lower levels, and there's resistant in you all. 97 present
- then you all 54 mutations can occur, and those can cause costs cross-resistance, because those are mutations at the viral DNA polymerase where fast carn it's it's it's over and again. Cyclover. All act
- Now when you. It's easy now to do resistance testing for Cmv. It's it's done
- genetically, so it's not a phenotypic test to genotypic tasks. And so you can. You can see what the mutations are, and typically you get things like this: a 460 V, which usually are higher levels of resistance. But if you have less than fivefold resistance, sometimes you have the option to overcome that resistance that that a level of resistance, using higher doses of either can cyclover or vogan cycle here. Typically, we do it. Iv. At that point, often getting 10 milligrams per kilogram twice day instead of the standard dose, which is 5 milligrams per kilogram twice a day. But when Cmv. resistance does occur it's really a difficult problem to

treat. But now I think it's getting easier, as I'll show you later as we move into looking at some of the newer drugs. But this is a patient that I treated. I guess about 1012 years ago, young man, with cystic fibrosis who developed over time multi-drug resistant Cmv. When you see those mutations there, so kept getting more resistant, and we got all sorts of different drugs through investigational or emergency use of drugs that weren't quite licensed yet, like

- cmx o one, it was called. Then it became brinced doof of here, which we actually we're able to use for a number of years. It's a lipid conjugate version of sedophobia. that doesn't have the kidney toxicity associated with Sudo, for it has some gi toxicity, and the company made it available for many years, but perversely it got FDA approved for smallpox. That's not perverse, but the perverse part of it is now. We can't get it, even though the Government has
- hundreds of thousands, probably of doses of it in case there's effort. Like a smallpox outbreak, especially involving the military, they basically finance most of the development of this drug, and it's probably a pretty good drug for AD no virus. It has some other roles, but I've tried a number of times and it's a weird approval based on efficacy and animals that that specifically doesn't allow it to be made available. And so it's kind of a weird situation. And then this drug finally actually seem to work in this patient. If you look at the Ct. Scans, you can see those little kind of nodular disease that improved, and this kind of heaped up lesion and the colon that improved and this drug, this bike 246 is actually the term of here. It was a German company, a curious that developed the drug before they sold it to merck and that actually worked at a rather low dose. And I'm not here to tell you that lithium is a good drug for people with difficult to treat multi-drug resistant cmv. But it may have worked in this case.
- So this is an algorithm it's no longer entirely up to date, because it doesn't include Rebecca, and maybe the term revere in it. But it's still useful in terms of when Cmv. When you want to suspect the Cmv resistance, and then looking at the mutations, and whether you can overcome those, perhaps with higher doses of of vulgar and cyclvere. but even when these indications are met like ongoing even increasing viral loads on treatment. Oftentimes, when you look, you don't have resistance. So the first thing you want to ask why you wait for your resistance has to come back? Is the patient absorbing the drug? Are they taking the drug sometimes switching? If they're hospitalized in particular to intravenous against like liver from can vow against like over will take care of the problem. I recently had that experience in someone you had some theesophagitis, and was just having a terrible time swallowing the valgant cycle there. the saphagitis was actually from Cmv. so sometimes changing to intravenous treatment, will take care of it.
- reducing the immunosuppression when you can in a STEM cell, transplant with bad graph for's host disease there often isn't a whole lot of distance. You can go there, and solid organ transplants Many people will hold the anti-proliferative which usually would be something like Microphentylate there are a number of other unproven or investigational options. the term of air is actually one that I would call unproven or investigational in this circumstance for resistant or refractory disease actually has that indication. So they were approved for resistant refractory disease, although there's certainly are many limitations to that drug.
- there are adaptive t cells that are potentially available. I'm not going to get into too much detail about that, and we'll talk just a little bit about Cmv immunoglobulin.
- So let's talk about ribbons for a second. So one of the nice things about both from Heruba Van La term Revere is that they Don't act at the level of the DNA Polymerase, and they don't

require phosphorylation so there is no cross resistance between Rebevier, the termavir and the drugs that we normally use gain cycle of air, fast carnage, and sedolfavir. Now.

- the mechanism of action of marijuana is that it prevents it. It does act at you all 97, but it but the mutations that create resistance against likely or don't create resistance to
- but it prevents that phosphorization which makes it such that the developing virion can't leave the nucleus because of that mechanism, though it is antagonistic with can Cycllevere, so it will prevent the activity of you all 97, and that phosphorization is required to activate gain cycle of here. So you wouldn't ever want to use those 2 drugs together. it doesn't have activity against most other double-stranded DNA viruses so if the patient has indications for
- prophylaxis against Ver cell disaster or Herpy Simplex. Then you'd want to put them on a cyclover or Valley Cyclvere.
- there are some drug interactions, probably not as much as the termavier, but it is a weak inhibitor of the sip 3, a 4 system, which means it'll raise your calculation inhibitor or empor inhibitor levels which are often used as immunosuppressants and transplant patients.
- It was in it was FDA approved in 2,021, and you know
- kudos to the, to the pharmaceutical companies. It was Shire and Tikita who went down this pathway because studying resistant and refractory disease and getting an indication for that is really is really very, very difficult, and they are working on an indication, I think, an indication. They're certainly doing studies for preemptive
- therapy, which I'll talk a little bit about as well. So the development of this drug really went on for a long time, and early on they were actually looking at it for prevention. So there's nothing necessarily, I think, unique about Rubberville versus the term of here in terms of what indications they wound up. If it more had to do with the desires of the people paying for their development. but it did kind of fail as a prophylactic drug which would be the easiest thing for a drug to do right. It's a lot easier to prevent an infection than it is to treat one but that was probably because they just do it too low.
- And as they later on found that the need for a higher dose, they moved on and use that dose in their resistant refractory trials. But there is some data for using it in preemptive therapy. That's where, again, rather than put people on universal prophylaxis who are at risk. You follow their viral loads.
- and there is a study from a couple of years ago, of wherever for preemptive therapy. It's Currently it got license at the 400 milligram dose, but this one looked at 4, 8, and 1,200, and it wasn't any different than Val, site and solid organ or STEM cell transplants, who generally had
- pretty low viral loads there weren't many in this higher range in this group, but of concern, while there was less nutrients with Vulcan, cyclover, and this drug is really well tolerated. and as oral, there were 2 patients on Ribavir, who developed recurrence on drug.
- and had documented resistance. And there are real concerns about what the buried or resistance to revive is some of those concerns came out in this study. We participated in this study, which really was just the taking resistant and refractory cases. There was no control arm just trying to figure out a dose. So they did. 400,000 801,200 found the foreigner. Dose was fine.
- but I noticed that a third of the patients
- develop Cmv recurrence on treatment. We don't normally see this in people on Val against like live on fast card at once. They're undetectable on treatment they usually stay there. Now

it may depend on the assay you use, but at this time the essays weren't as sensitive as the ones we use now. So that's concerning treatment emergent resistance, and raises questions about the buried or resistance of this drug.

- But they did move forward, and they did the solutions trial. Robin Avery at Johns Hopkins was the lead
- investigator. On this I mean it was a pharmaceutical, sponsored trial. The multi-center trial which gave 8 weeks of ribbon to people with resistant or refractory disease versus investigator
- assigned therapy.
- So you could pick foscarnet, high dose scanned cycle there, or sidophobia, or some combination, and if you failed, those or couldn't tolerate them after 2 weeks you could switch over to a rescue arm when you got more rib ofier, so there was no mortality benefit to them, Riviera. But that's kind of expected, because
- and many of the patients in the investigator signed treatment did flip over to the rescue arm, and it was a mix of STEM, sound, solid organ transplants. And You can see that about 100
- 56% on ribbon at the primary out point endpoint. And that meant that they were basically undetectable at 8 weeks. That was the period of treatment. Now for those on treatment. This is an intention to treat analysis. Those on treatment. 70% were actually undetectable at 8 weeks. Now
- you look at that. And then you say, okay, what happened at 16 weeks. So they're off drug for 8 weeks. and what you see is that only 18% remained undetectable in the move of your arm. And I don't think that's actually because
- the drug doesn't work, it's because they weren't on it anymore. And 8 weeks is not enough, that's all it's telling us is that you have to treat people for longer, because the recurrence rates are so high with Cmv, particularly in this population. That's a real challenge, because the drug cost as much as $30,000 a month. So
- getting that that paid for longer than what it's licensed for. It can be a real challenge. This is just another way to look at that in the solstice trial. This is patients with response, meaning and undetectable.
- Cmv. viral load. The Red X indicates where treatment was. was stopped. Then you can see, as anyone who takes care of these folks will tell you, you know, when you stop drug, they often get virgin make again. Now some of them will get via remote and control Cmv on their own. Because, remember.
- we're not trying to cure Cmv. You cannot cure Cmv right. It's a latent virus. It's going to stay there. We're trying to control it and give people a chance to develop their own immunity so they can control it themselves.
- And then over time you can see as you get to week, 16 and week 20, it kind of leveled out in terms of the people the number of people that were relapsing.
- and this is just from another trial. It's called the impact Study, which just compared Valg and Cyclo To intervene is grand cycle there for non resistant or refractory. So much easier to treat people, and even in that circumstance, after 49 days of treatment you get a 15% or so relapse, so it's not surprising that that relapse was observed.
- What about tolerability? So the main side effect of ribavir is disguise. What people tell me is, they get a metal taste in the mouth. Fetch it just just bad taste in the mouth, and so that, you know can be a significant

- A problem but rarely leads to discontinuation of treatment. and I've had a few patients who seem to have pretty bad nausea with it, so that that can happen as well. But one of the key points for both ribbon and the term of here is that
- They're just really well tolerated. Otherwise. So when you compare it to the investigator. Assigned treatment in this case, whether it was fast carnate or Valc Encyclopedia, you get all this neutropenia with again, cycllevir you get a lot of of renal disease with fast carnet, and you just don't really see that from Rebecca.
- So kind of conclusions on marijuana is that you don't see the Hemith Logic toxicity compared to Valg and you don't see the renal toxicity. You do see sometimes this disguise.
- but it does have some drug interactions, as I mentioned before. and the main thing I'm worried about with Rebecca is
- these hints and more than hint of on treatment, resistance, and failure occurring which we wouldn't have expected with our older drugs. And so it may not be. It may not have as a good a buried or resistance as some of the older drugs. And so
- I still very concerned about using this when the Cmv. Is quite active. if there's a lot of end organ disease, and in hospitalized patients in that circumstance
- I would rather try and get their viral load down, get them treated with fast carnet when their viral load is lower. Then try and switch them over to the to the rib of here, because I'm worried about resistance developing. And then you're going to lose the ability to use that drug later. Occasionally you'll have people who's.
- you know. Creating is 3.5 at Baseline, and you feel a little nauseous yourself, giving them a drug like fast carnet, which is so enough for toxic, so you can argue that one back and forth. But, in general, if you can, I would rather use fuss carn if there's just you all 97 mutations.
- and or you all 54 that don't create fast carnet resistance and then use river after you've got the viral load down, and when you know when you're looking at something that's priced at $30,000 a month. You're gonna have some problems with paying for that. So that's another challenge, especially when you want to use it for for longer than it's been
- sort of approved at 8 weeks since we know 8 weeks won't be sufficient.
- So we'll move on to the term of area. The terminator also has its own
- mechanism of action. it inhibits the terminates complex. So kind of the final steps and processing virus. And at first there was kind of concerns that
- there would be a real delay in seeing the viral load go down because it's not stopping you from making Cmv. It's stopping cells. it's just it's stopping Cmv. From fully maturing. It is being released into the blood where you can measure it. But they're not able to infect other cells, but that Hasn't really turned out to be much of a problem
- like Marijuana. It's extremely well tolerated with limited
- hematologic or real toxicity. There was a few things like Hl Orythmias, which I don't think of really panned out reporting in the licensing trial. but it's generally very well tolerated. There's an intravenous and an oral formulation.
- There is some issues with bioavailability. So in healthy subjects it
- it kind of look like Val site where you had, or drugs like Lena's lid, where you have really good bio availability but that didn't show up as well when they looked at some pharmaco kinetic studies and STEM cell transplant recipients. So some of the breakthroughs that you may see with the term of here, are related to

- probably, how much drug is getting absorbed. It's a clear hepatically.
- there's no dose adjustment for Meals failure there, Aren't. Clear directions in human dialysis. But I actually think you probably don't really have to change the dose. that's an off-label thing to do. But again it's not a particularly toxic drug.
- There are drug interactions with it. you're gonna end up
- decreasing your calculation. And inhibitor by about 50, and probably your Mtor inhibitor by a little bit more. If they're on those drugs. and that's because it inhibits the sip. 3 a. Some of the sip, 3 a isil enzymes that metabolize
- those drugs. It also has some weirder drug interactions. It's a substrate of this organic anion transporter and cyclists born inhibits that or competes for it. I'm not sure which. But either way, if you use it with cyclists, foreign, but not Tack Row, you actually reduce the term of your to 240 instead of 480 milligrams.
- It also lowers for a consol levels which isn't intuitive since it's an inhibitor of see sip 3 a 4, but if they're on voicemail you need to
- make sure you're doing therapeutic drug monitoring of the voicemail.
- So the licensure for cmv this was from 2,017 is for prevention of sorry. The licensing for the term of areas for prevention of Cmv. And Ser. A positive
- STEM cell transplant recipients. Our STEM cell transplant is like to give it to 0 negative people as well, so we have to stop them all the time, because it's not really necessary in that circumstance, and it is expensive. It's about $200 a day.
- but what you see is a significant reduction in Cmv. Events. People got it from soon after transplant. I think it was out to 14 weeks or so, and where you see, this increases when they're off the term of here. Those that are largely are getting graphers, host disease getting immunosuppress. Their Cmv. Is reactivating. And so
- many centers we included. Try and continue it in people who have graphics, host disease, and there are studies looking out at
- doing it for 200 days instead of a 100, and that that's probably where it's going to wind up, particularly in those who are requiring significant extra, you know, suppression for graph first host disease, and there may even be a little bit of a mortality benefit. it didn't pan out at later endpoints. But it was mostly seen
- interestingly, and those who actually had clinically significant. Cmv. You'd think it'd be through prevention of Cmv. If there was any mortality benefit.
- but it may be because it delays Cmv to a less vulnerable time, or that the Cmv. Is somewhat attenuated on term of here. I don't think anyone can say for sure, but it's kind of an interesting analysis.
- in terms of resistance. I'll just say what term of here has a pretty low barrier to resistance, and those resistant mutations. Don't seem to have much impact on viral fitness. so it doesn't really slow down the Cmv. Much when it gets resistant.
- and there was hints of that in the initial trials of the term of here, and we actually learned that, you know we don't check Cmv Viral loads and STEM cell transplants early. but
- when you participate in these studies and you get the baseline, cmv viral loads done, you'll find that they often are by Remake at a week or 2. We'd probably rather not know that in the past, because, you know, treating it as pretty much impossible. Then, without doing things like

fast carnet, which you just don't want to do that, and they don't get clinically significant Cmv. Disease early, except in very rare circumstances.

- so when the term of your came out, we didn't have ribbons. People were looking at, hey? Can we use this drug for treatment? when we're kind of out of options, or our options are so toxic that we don't want to use them. There's a whole bunch of case reports. But here was one from Duke that looked at
- for I think they actually up to 6 now.
- with Cmv. Retinitis, because it does actually get into the I and the patient I showed you earlier did have Cmp. Right? It's the one I treated a number of years ago, and it did respond actually to the term of here and there retinitis improve, but to develop resistance. 3 experience viral rebound. Nobody knew what dose to use. The standard dose is 480,
- and they just kind of analyzed it and said, let's use a higher dose. So I don't think it's really a reliable drug for people with significant Cmv disease. We took a look at that. We looked at 47 patients that were really a mix of
- STEM cell and solid organ transplant patients.
- About a third of whom had resistance or refractory for other reasons, and about a third had end Oregon disease. Many. It had multiple episodes of Cmv. So a really heterogeneous group where people were just kind of reaching for other therapies, most got the standard dose of
- of. And data like this is really hard to analyze. But, I I think the general lesson that we had at this time is that
- there weren't a lot of on treatment
- breakthroughs of Cmv. When it was started in people with low viral loads, recognizing that a viral out of 1,000 at one institution may be very different than a 1,000. Another institution depending on the as you use. But nonetheless, once you got disease under control a little bit with something else, or maybe you caught a rebound or a relapse. Early.
- Most people did okay with the term of here.
- however, when it was given to people who had more significant ongoing disease and higher viral loads at initiation
- outcomes were variable. There are some people, and there's one paper and lung transplant patients where people did very well. So sometimes you can get away with it and give people the term of here who have Cmv. disease that's significant, and it'll work, and they won't develop resistance, but you can't rely on it, and it's certainly not the first option.
- this was just presented at at this last Id week in October. which is another indication for the termavir, which is primary prophylaxis and solid organ transplant recipients.
- and what they did was universal prophylaxis. What term of here for 200 days versus valg and cyclover for 200 days and 600 high risk kidney transplant recipients. And you can see there was no difference at a year
- in Cmv disease, but it was less toxic. So Neutropini is a huge problem with Valg and Cyclover. and you can see the rates of nutrientia. We're much higher with Valg and Cyclover, and led in some cases to treatment discontinuation. So I think this is going to be
- an exciting option for people who develop cytopenias on valeg and cycle veer during the prophylactic purse period. If if they go ahead and get if Mark goes ahead and gets an indication which I assume they will try to do for primary prophylaxis for

- high risk after solid organ transplant, so we'll see if they move forward with that. But I think that'd be a nice option. The cost may still be an issue. So in summary on the term of year, so approve for prevention of Cmv. And STEM cell transplant
- patients, but very little data for treatment, and clearly, sometimes they're going to develop resistance if you try and use it for treatment. So again, if you're going to wind up doing that
- you're probably going to want to try and get the viral load down with another more toxic drug like fast carnet and then switching them over because the term of area is quite well tolerated, and it's actually sometimes easier to get them rib ofer because
- they kind of have a seem to have a better
- program from the pharmaceutical company to pay for it. If they don't have a government pair and it's also a little bit cheaper. It's still very expensive. It's like, I think, a couple of $100 a day, but it's still less expensive.
- So if we compare these 2 agents, both of them have unique mechanisms of actions.
- Both of them lack hematologic or renal toxicity, which is kind of the bug of who they are currently available drugs. They're approved for different things, maybe not so much because of the properties of the drug, but maybe just because of the way the companies approached it. But maribavirus for resistant refractory disease.
- The termavir is, prophylaxis and STEM cell, and maybe soon as higher as solid organ transplants.
- Clearly, the term of here is a low barrier to resistance. I suspect the same is true of Marib of air, but the information for that is is a
- less robust.
- So you know, when you think about
- low barrier to resistance, you think about using multiple agents right? We don't treat people with HIV with one drug. We know that in most cases they'll become, or in many cases they'll become
- resistant. What about using the term of your with marijuana we already mentioned? You can't use river and can cycle there, and many of these patients already have Gincyclavia resistance, so there are a few case reports. Mechanistically they work at different points in the viral life cycle. So from that perspective it's a reasonable thing to do.
- Trying to obtain both drugs is difficult. I don't know, since they're made by different companies, that anyone will ever study this in a way that gives us any reasonable information. But this is something I would love to do if I could get both of them in in specific cases where you knew you were going to face a challenge.
- I'll just mention a couple of other things in the last few minutes that we have about trying to prevent
- Cmv resistance, because obviously resistant fires is very difficult to deal with as do many places. We had a significant problem with Cmv. Resistance in our lung transplants, often with multi drug resistant virus.
- and so one option we looked at was adding, cmv immune globulin, which is really just
- ivig from people who are Cmv. 0 positive it's FDA approved to reduce the risk of of Cmv. But Isn't used terribly widely for that. But we did go ahead and do that, and we've been doing it now for

- 6 7 years, and our high-risk lung transplants, don't or positive recipient negative we give the first 2 doses in patient, typically the last 4 given outpatient. We've had much less problem with Cmv resistance. Now. Part of that might be because we've really emphasized
- Don't dose for Zoos, your valg and cycle of your prophylaxis. I wouldn't do it in any lung transplant, and I wouldn't do it in donor positive, recipient, negative, solid organ transplants. There are many places that use half toes, valeg, and cycle. There's prophylaxis, but I would focus that on low risk Risk patients.
- So we have a nice protocol for dose reduction for Lucapenia, which focuses on switching over to preemptive therapy where you're just measuring the Cmv Viral loads weekly or holding the other drugs that contribute to the site of Penias, the microfinance and the is a thipr, and soon, I think.
- using L term of in this circumstance
- would be very reasonable to with the data that now exists if you're able to obtain it.
- and just a couple of final points about other things to think about with resistant Cmv is that can cycllevair levels when given it, especially as a vague and cycllevair can vary quite widely interestingly at standard dosing you actually get more exposure
- mit
- in the a, you see. So in an individual, you don't know exactly how much you're getting, and I think this was. I think it was that. Well, it did a very nice but very labor-intensive attempt to really target based on fine distinctions and renal function.
- they're again Cyclvere and Valg and Cyclover dosing, and they had quicker viral clearance and and and fewer relapses. it's something that's very difficult to to do. But it's interesting to think about an individual cases where you're struggling.
- and finally, I'll just mention with M. Tour inhibitors and Cmv. Because people often like to switch to an Mtor inhibitor. when you have kind of chronic ongoing problems with Cmv. Because there is data that Cmv
- occurs less commonly in people who are receiving M. Tour inhibitors, whether people who are having an actual problem with Cmv. Benefit from changing their
- immunosuppression, to include an Amd or inhibitor, I think, is less is less worked out. But it is a strategy that that some people employ when you get a little bit desperate hopefully with these new drugs we won't have to do changes like that quite as often.
- So in in summary resistant, refractory. Cmv, you know, remains a a a really difficult problem to treat, but having Rubberville approved, is a massive advance, I think, to have a well tolerated oral agent. But again.
- often I would try and get things under a little better control with Foss card and then switch over to them. Rivier.
- term ofer would be a little bit of a distant second choice in that circumstance. But I think it can still work if you can't get moreibbe, or you can't continue to get more of a beer. but only really a step down therapy when you've already got the viral load down.
- I'd love to know more and learn more about combination therapy, particularly lieutenant, the term of your and ribbon. But that that those kinds of studies may be difficult to actually get done.
- And again, the best thing I think you can do to reduce your rates of drug resistance. Cmv. Is to be

- to be careful about dose reducing it in higher risk patients. And with that I'll finish. And thanks for your attention.

UVA Medicine Grand Rounds

01:07:58

Awesome.

- Yeah, Thank you so much. Dr. Call. That was a great talk. I'm gonna open it up to questions, both to people here in the audience and on zoom. I'll get things started, you know one of the things that kind of struck me was just
- what what can we do for the donor, positive or recipient negative, solid organ transplants prior to them getting a transplant. So I did wonder if there is any conversations you would kind of briefly mentioned maybe teaching t cells to do something, but or any conversation about Cmv. Vaccines
- for patients who are undergoing a transplant.

Daniel Richard Kaul

01:08:36

That's a that's a a great question, and there is a

- an niad funded study. We're we're part of it the person who did the preemptive therapy study at the University of Washington Git Lemay is really the leader of it to do vaccination prior to liver transplant.
- and then do pre preemptive strategy and compare those that received active vaccine versus a placebo, because I think that's a great potential solution. There have been other companies working on Cmb vaccines largely focused on a bigger market which is pregnant women.
- One of the problems with doing the trial is, you don't know who is going to be
- high risk until they get their Oregon allocated. So you have to enroll 2 people for everyone who's going to enroll, because you don't know who's going to receive a negative Oregon. there are, an M. I'm sorry a positive organ. There are.
- moderna is working on An Mrna Vaccine as well that may work. So I so I think that that would be an ideal solution, Much better to give somebody immunity pre transplant than to have to
- deal with all these expensive prophylactic agents and all the indirect and direct consequences of Cmp. Infection. Great question. Yeah.

UVA Medicine Grand Rounds

01:09:59

I guess in the same vein. Is there any way we have we ever tried to treat the organ itself.

- You know. It's hard, I imagine, to take a very sensitive time-sensitive and then sensitive piece of tissue, and do anything to it before you put it into someone's body who needs it.
- I don't know if you know of anyone who's trying to actually treat the organ that's positive to reduce the load.

Daniel Richard Kaul

01:10:19

Yeah, I don't know of any way Easy way to do that. I mean, there are. There is more like X vivo tuning of organs that goes on. We do that here some for lungs where they got.

- They get put on a machine, and, you know, sometimes treated with antibiotics and things like that. And but I think if you think of the biology of where the Cmv's hiding and lymph nodes, and other things kind of stuck on there. I think it'd be pretty hard to do anything in the timeframe that you had available. Yeah it. I guess you can't just massage it out of it just got to talk to it. Nice. Yeah, yeah, exactly. let me see if we have anything questions here in the chat. I think you can see the chat as well. let's see. We just wanted to make a few points, or at least in the beginning.
- Can you see that? Yep. So coasty, says, and you're so lucky to have coasty. He's just brilliant. I've worked with him in the past. So If you ever want to come to Michigan coast to there's always an office for you. Targeting was last performed at Uva for lung transparency, if it's in 2,010 since then no targeted acceptance based on 0 status. Yeah. So that I mean, that goes to the point that you know it's fraught right? Because you're you're removing the availability of a bunch of organs from people, half of them. But at the same time. I mean, if I was Cnb. Negative and need an organ. I'd much rather get a negative one. And then there's another question I this has been discussed in lung transplant for ild patients with short telomeres. I think they meaning the serial sorting, I think. Yeah, I think so.

Unknown Speaker

01:12:01

Yeah.

UVA Medicine Grand Rounds

01:12:02

Daniel, Can you hear me?

Daniel Richard Kaul

01:12:04

Yeah.

Costi D. Sifri, MD

01:12:05

Good to hear from you, Dan. That was fantastic. thank you so much for joining us virtually. And next time the scenario is on me.

- I did have a question. we do also have some experience with river beer we weren't involved with the clinical trial, so not as much as perhaps your experience, or almost certainly not as much as your experience. but we, too, have had the challenges with what we are proceeding as a fairly low barrier to resistance. I'm curious about your thoughts and experience on, treating with alternative agents before switching over to Marijuana beer those situations where we can tolerate an agent lock post car in it for some period of time for erez agmoni for the term of year. I think we Our practice is pretty similar to a lot of other places where we try to you know. Treat a patient within 150 for drug resistance. Cmv: until they're undetectable. you know, 2 times in a row, or perhaps have a very, very low amount of a detectable virus on our assay, which is the avid essay what is your switch point? do you have one in mind when you're sort of having a similar thought with.

Daniel Richard Kaul

01:13:23

Yeah, so we do the exact same thing. I I think if you give somebody, you know who's let's say, got you know you get these folks who just gets missed for a while, you know. There's all sorts of stories and reasons, but somebody comes in with like for me, I mean. I just had one who had like 4 million copies, and had actually had probably encephalitis with Cmv. I mean he had a viral load in his Csf, and he was confused, and there was nothing else, you know. So I think if you give somebody like that, and you got maybe a 50 50 chance at best. You know of success, for the reasons that you said that that it probably has a low barrier to resistance. I mean there's just a pretty good hint of that, and if you look through all the different trials that have been done on it, so I would much rather give them fuss, Carn, and if they had resistant virus

- try and get them down that way. And so when do I switch?
- You know? I I think you know, and we use the same asset, and I think it's the same reagents now, because you have to buy the reagents. You know it. It. Maybe 5 6 years ago it changed where you know there was. You had to use. The FDA approved reagents on that machine, and our viral loads went up tenfold when we did that, actually. and so I would like them to be below a 1,000.
- Some of that's just based on our series with the term of year. and I would like their end organ disease to be better. But I kind of kind of go by their kidney function, too, you know, when it's when they start to have problems with the Foss carn. It seems like a reasonable time to

change. So I haven't had anybody develop revere resistance doing it that way, you know, so far. And then the problem, of course, is just how long can you get it, Forum? Afterwards? I have one who's at our Va. So the Va. Is paying for it, and then they you know, they ask me every 2 weeks. Do you want to get more, you know, and it's just because it's just so. Darn expensive.

- Have you switched over to the term of your in this situation I have, because, especially if they have commercial insurance, Mark is extremely generous with the support, and I had one a couple of days ago, and I couldn't believe it. It just came back, and they just, and this was someone who was more. It's more. He didn't have resistant virus. He just was. Had
- he's liver transparent. So at a big spleen, you know. His white count was 1.5 at Baseline, and he had to come off prophe for that reason, and got cmv because he wasn't he lived in a rural part of Michigan, and he wasn't getting properly monitored, and so forth. And
- in 4 h, they said, approve no copay. I have no idea why
- you know it's it's like there's a random wheel at the insurance company right that they just spin, and I got lucky on that one.

Unknown Speaker

01:16:02

Hmm.

UVA Medicine Grand Rounds

01:16:06

Well, very good, all right. I think there's no more questions here in the chat. I don't see any questions that people here in the audience. So I just want to thank you again for a fantastic talk about a very complex disease state. And we're happy to have you back anytime.

Daniel Richard Kaul

01:16:21

My pleasure. Thanks for the invite. Take care, take care, bye.