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ALFREDO CLAVELL: Hello, and welcome back to the Mayo Clinic Medscape video series. I am Alfredo Clavell, assistant professor of medicine at Mayo Clinic and medical director of our heart transplant program. Today we will be discussing medications to improve heart transplant outcomes, sirolimus and beyond.

I am joined by my colleague Dr. Sudhir Kushwaha, professor of medicine and an expert in this area. Welcome, Dr. Kushwaha.

SUDHIR KUSHWAHA: Good morning, Alfredo. And it's good to be here, and we can have a good conversation about this.

ALFREDO CLAVELL: This is great. I know we've talked about this in our clinical practice often with the whole group. But today I want the audience to hear a little bit about why we're using sirolimus, and what are the advantages and, perhaps, disadvantages, et cetera. So we'll start with what is the history of sirolimus used in the Mayo Heart Transplant Program.

SUDHIR KUSHWAHA: Well, there's an interesting history. I mean, sirolimus, otherwise known as rapamycin, has been known for many years to be a powerful immunosuppressive, antiproliferative drug. And so, first, it was thought to be an antibiotic, but then its immunosuppressive properties became apparent. It's a fungal derivative. It was discovered on the island of Rapa Nui, Easter Island. And initially, it was known as rapamycin. And then when it became commercialized, it became known as sirolimus.

Now because of the basic science data which has been there for many years and the known effects on certain pathways which cause suppression of T cells, years ago, back in the early 2000s, I thought that it would be a good and interesting perspective to look at whether or not we could use these advantages, these known antiproliferative, immunosuppressive advantages in our program.

And the reason is because heart transplant outcomes are really affected by a number of factors, one of which-- most important of which, probably-- is cardiac allograft vasculopathy, which is otherwise known as transplant-related coronary disease, which is known to be a highly proliferative process.

So we started initially with a pilot study back in 2003, we were just looking at 12 patients in whom we looked at renal function, predominantly, because renal function is also a problem post hoc transplantation because of the immunosuppressive drugs we use. Tacrolimus and cyclosporine, which we were mostly using in that era, suppress or cause degradation of renal function over time.

So the first-- this pilot study we had of just 12 patients was really aimed at looking at renal function. It was a one-year study. And we demonstrated that renal function improved in a group of patients in whom we targeted for sirolimus use. So that's how it started.

And then when we developed experience with the drug, and we realized that patients were actually doing quite well on it, and they weren't developing rejection, we extended the study to look at the most important long-term determinant of survival, which is the transplant-related coronary disease. And we subsequently went on, started putting more and more patients on it, and had a number of publications too which demonstrated that patient outcome and, in particular, allograft vasculopathy, was suppressed by the use of this drug.

ALFREDO CLAVELL: And you have covered, I think, already, some of the advantages and disadvantages of the standard immunosuppression versus the new kid on the block. We've had 20 years' worth of experience with sirolimus. And would you care to comment in terms of how many patients in our programs are managed with the sirolimus, percentagewise? I mean, is this well tolerated? Are there side effects? Are there concerns?

SUDHIR KUSHWAHA: I mean, the reality is, Alfredo, that all the drugs we use are toxic agents. We're dealing with immunosuppression to suppress rejection of the transplanted heart, the consequences of which would be catastrophic. And so standard immunosuppression presently consists of tacrolimus, mycophenolate, and steroids. And all of those drugs have side effects in themselves.

Sirolimus is no exception. It has a unique set of side effects which are different from tacrolimus, but they're still somewhat unpleasant side effects as well. But it's a case of, which poison do you pick? And therefore, which side effects do you pick?

So whereas tacrolimus can cause hypertension, headaches, tremors, a variety of other side effects, sirolimus, on the other hand, causes mouth ulcers, sometimes peripheral edema, GI side effects. But the way we get through all this is that usually the patients get used to the side effects to a certain extent. And actually, over time, they tend to diminish.

In our program, I would say, right now, we have about 60% of our patients who are primarily immunosuppressed with sirolimus rather than tacrolimus, in addition to the other two agents which I mentioned earlier.

ALFREDO CLAVELL: Correct. And we have found the experience with this particular agent to be quite gratifying in a number of personal cases. One thing that I think we like to point out is that it's something we start later in the process because it also has would healing-- it affects--

SUDHIR KUSHWAHA: That's a very important point. The very antiproliferative properties we take advantage of in suppressing allograft vasculopathy, and then also cancer, which we'll discuss a little bit later, is also a downside of the drug, because it impairs wound healing, because for wound healing, we need proliferation to occur. And so a drug which suppresses proliferation is also going to suppress wound healing.

So we didn't start it de novo upfront, immediately after transplant. We tend to wait until everything is healed up, typically six months. But in some patients who might require intervention earlier, we might go to three to four months.

ALFREDO CLAVELL: Well, let's delve into the most important thing that we want a rejection drug to do, which is prevent rejection. So are rejection rates any different with sirolimus? I mean, have we observed any significant difference between tacrolimus, cyclosporine, or sirolimus?

SUDHIR KUSHWAHA: Well, the short answer is no. Their historical perspective is that when we first started using sirolimus, we were very worried that people were going to come in with severe rejection. In that initial pilot study, there was no difference, but that was only a very small series. And then, subsequently, in our larger studies, when we've looked at rejection rates, treatable rejection rates, there's really no difference.

Now the reality is any patient can reject. It doesn't matter what immunosuppressives they're on. And we have a surveillance program looking for that, specifically. But we've looked at this at least four times over the last several years, since we started our program. And we haven't found any difference in rejection rates. And that is gratifying because it would be a major disadvantage if patients were coming in with catastrophic rejection which could result in a poor outcome. Obviously, we don't want that. We want a really good outcome for our patients.

ALFREDO CLAVELL: Now of course, a lot of that has to do with the fine tuning of the program and how do we transition from cyclosporine, tacrolimus, which is mostly what we used, to sirolimus, and that gap and overlap for several weeks on both drugs as we get one down and put the one other to prevent precisely the rejection. So that's really the most important thing.

But now we're talking about changing the side effect profile. And I mean, I think the audience is well aware that sirolimus is commonly used for coating stents, the more recent stents are covered with everolimus to prevent the proliferation from stents. And so let's delve into the transplant vasculopathy. How has that affected our transplant vasculopathy as we transition more and more patients to sirolimus?

SUDHIR KUSHWAHA: Well, we have, I think, demonstrated in the published literature that our allograft vasculopathy clearly come down. There's no doubt-- I mean, the data is overwhelming and very strong. And in addition, we've demonstrated over a lengthy period of time, 12 to 15 years now, that overall survival from all-cause mortality improves as well.

So the suppression of the vasculopathy results in improvement in long-term survival. So if we look at the ISHLT database, which really covers all the data worldwide in all transplant patients, and look back at the survival curves, which understandably includes some historical data, we see that the 10-year survival, on average, if we take the history of heart transplantation, is about 60%.

Now if we look at individual programs, we see that that rate is maybe more like 65% to 70% 10-year survival. So it's not very gratifying if you're a patient who's 25, and your doctor says, well, actually-- or the patient themselves looks up these days before they come into the doctor's office, and that's a far more common scenario. They look up, and they say, well, there's a 60% chance that I might be dead in 10 years after heart transplant? If you're 25 years old, that's not really very good news.

And so what I think we will find, as we extend out another decade or two, that we will see more and more long-term survivors. And there are a handful of patients in our program-- admittedly anecdotal, so we can't really project their data to a broader cohort-- but there are a handful of patients who we converted early on because they had vasculopathy. And we expected them not to do well. And they weren't re-transplant candidates. But those patients have actually continued on a decade later with angiograms which really haven't shown a huge amount of progression in disease.

ALFREDO CLAVELL: Yeah, and the big emphasis, I think, you pointed out for the benefit of the audience is that the sooner you start the sirolimus, the transition, the better the outcomes. Of course, when we started doing this, we were putting patients on that had been already several years on that. But we found always that the sooner you start the medication-- because I think a lot of programs wait till they're having a problem to consider transitioning. And although that strategy may be helpful for that particular patient, a strategy of transitioning most of everybody early on is probably a better strategy.

SUDHIR KUSHWAHA: And that's absolutely right, Alfredo. It's a very valid point. And in fact, that's one of the main points we made in our publication which looked at a long-term cohort, that the earlier the conversion, the greater the degree of allograft vasculopathy suppression.

ALFREDO CLAVELL: So we have benefits in the disappointing rate of renal dysfunction that we invariably see with the calcineurin inhibitors. That's sirolimus and cyclosporine. We have seen benefits in allograft vasculopathy that translate into better survival, because transplant allograft vasculopathy is a major cause of morbidity and mortality as we get into the 5, 10 years.

But lastly, there is a unexpected finding that you published a landmark paper here recently in terms of malignancy rates in the long term following the sirolimus-converted patients and how is that affected, because we know that malignancy is also another major source of morbidity and mortality in transplant patients.

SUDHIR KUSHWAHA: Correct, and that's a very good point. I mean, malignancy, vasculopathy are the two major causes of mortality. And the reason transplant patients are prone to malignancy is because the immune system, which we need to prevent infection, also, under normal circumstances, deals with cancer cells, aberrant cancer cells which our bodies are producing all the time.

And we're suppressing that immune system, so what we've seen across the board with all solid organ transplants is that if you suppress the immune system, you're going to have an increased rate of cancer. And there are two types of cancer. A common type is a variation of a B cell lymphoma. We call that PTLD, or Post-Transplant Lymphomatous Disease. And we're constantly looking for that when we undertake surveillance on our patients.

And then there are non-PTLD cancers as well. So the rates of both are increased in heart transplant recipients. And because the level of immunosuppression tends to be high in our population, compared to perhaps other organs which need less immunosuppression, our cancer rates are relatively high as well when we compare with the broad cohort of transplant recipients overall.

And so cancer is proliferative process. So in other words, for a cancer to grow and become manifest, it requires cells to be proliferating at a rapid rate, a high turnover of cells. And this is very characteristic with PTLDs. So you'll have a small collection of cells which will rapidly get bigger, and then manifest in the patient.

And so the initial studies using rapamycin in the lab showed that it suppresses these cells. And so we looked at this, and we looked at rates of PTLD in our traditional immunosuppression patients compared with the sirolimus-treated patients. And sure enough, there is a significant difference in cancer suppression.

And that translated not only into PTLD, but also into non-PTLD, and also other types of skin cancers, and a variety of other cancers, actually. And so I think that's another reason why patients-- that all-cause mortality is better as well. So it's the vasculopathy and cancer suppression. So I think that it really makes a lot of sense to be using this approach to immunosuppression in heart transplant recipients.

ALFREDO CLAVELL: Yeah, and I think it was originally sort of an idea born from the fact that we had a new medication that was likely to be effective. But now we've had 20 years of experience, and a number of publications are clearly documenting that sirolimus is a superior drug. If a patient can tolerate it-- and we talked a little bit about the side effects-- but most of our patients can with a careful transition.

And I think it's just great to discuss and enlighten everybody else about our experience with sirolimus, which was granted as probably the largest cohort of sirolimus-treated patients in the heart transplant population.

Thank you, Sudhir, for these very important insights. And thank you for joining us on theheart.org Medscape Cardiology.

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