[MUSIC PLAYING]

JAMIE PARK: Hi, everyone. Everybody's enjoying the program today? Yeah? So my session is the last one, but if you think about-- to turn your page to kidney transplant patient, evaluation to transplant may take only 18 months, but they have to live with this kidney for 10, 20 years. So I will be talking about what medications the patient needs to keep the kidney working for the duration of their life. So the patient is cleared, and Ted found acceptable donor, and Dr. Song did excellent job, so technically a successful kidney transplant. But what keeps the kidney working is preventing from having rejection.

So rejection after a kidney transplant can happen any time after the transplant. That is why our patients need to take their immune suppression, lifetime. Because basically, the kidney is a foreign antigen, and it is in their body, and their immune system will constantly recognize the foreign antigens and try to attack. And rejections can occur through deeper mechanisms. First I'm going to address is a T-cell mediated one. So this is the most common type of rejection, when we say kidney rejection. T-cell mediated rejection occurs in a highest rate in the first couple of months to a year. Dr. song mentioned about 20% of patients will have that. He's referring to this T-cell mediated rejection.

We have a great, very effective, T-cell targeting immunosuppressive agent. So if we catch it now, by monitoring creatinine regularly, and we do a biopsy, and we make a diagnosis all day and night, and we get more potent T-cell immunosuppressant, and we can reverse the pathway. And then pre-ban to them losing the kidney.

So most of times, the patient will regain their kidney function to their baseline. On the other hand, there's antibody mediated rejection, it can occur in two different ways. So Dr. Song mentioned the sensitizing event before the transplant. So that means the recipient develop antibody against the donor and his hands. So some of the patients, we all know, that they have a donor specific antibody at the time of the transplant, ready to recognize these foreign antigens as soon as we put the kidney in the body. So in those cases, if we keep proton immunosuppression at the time of a transplant, the patient will have hyperacute onset, antibody mediated rejection. In the old age, we call this one humera rejection.

On the other hand, even if your patient did not have specific antibody at the time of transplant, over time, they can develop the DSA, we call it duonoble DSA, and that lead to late onset antibody mediated rejection. So different from T-cell media rejection, this type is very hard to diagnose, and there's really not a good effective immunosuppression to block antibody production and the subsequent injury from DSA reaction. So this is a very challenging area for transplant nephrologist and other practitioners.

And the last type is our chronic rejection. Although it has a rejection in the name, it is not really solely due to immune media reaction. So typically, it resulted in gradually deteriorating graft function. It is one of the leading cause of graft loss. And ideologies and multifacortal, often unclear. And on biopsy, we just see a lot of scar tissue, irreversible damage. So at this time, increasing immunosuppression may not reverse the function. And eventually, the patient may need retransplant.

So we provide immunosuppression for lifetime to keep the patient live long with a functioning graft, without needing to go back to dialysis. But all of the immunosuppressive agents we use also have negative consequences, such as overall over immunosuppression will lead to infectious complications. They're at risk of developing cancer over time. It is higher danger in our population, especially skin cancer and other solid tumors are higher. And they also can develop lymphoma after transplant, as well. Each drug has side effects. So it is important to minimize, and we use lowest effective dose possible, to minimize drug toxicity.

So when we designed immunosuppression regimen, which include usually more than one drug, we try to use minimal effective dose possible, to prevent this negative consequence. So when we talk about immunosuppression, often you hear about induction maintenance , treatment of rejection. There are about 10 classes of immunosuppressive agents that I will go over in next 10 minutes or so. Some of them can be used for both the induction and treatment of rejection. Some are only for induction, and some are only for maintenance.

When we say induction immunosuppression, this refers to all the immediate post-transplant. So typically, we start induction intra-op, and during the preoperative procedure. And we usually use 3 or 4 drug combinations, and one them then is typically IV antibody. Because initially, we use a very high intensity immunosuppression, your patients risk of infection is higher in the first six months. So they will need antibiotics to prevent bacterial infection, antiviral agent, and antifungal agents for infection prophylaxis, first one to six months. And then they usually continue oral maintenance immunosuppression over their lifetime. We usually start at a higher dose and gradually decrease, to maintain the balance between rejection risk and infection risk. But they will never get off immunosuppression.

A lot of times, new transplant patient ask me, so I heard I'd be able to discontinue medication after a year. That is not true. I don't know where they got that, but they that is not true. Then how do you decide which one to use? There are a lot of clinical trials done in kidney transplantation population, they are very lucky. Heart and lung, very scarce evidence. So oftentimes, they extrapolate kidney transplant trials to their practice, unfortunately. But kidney, pretty much we based on clinical trial evidence.

We look at their immunological risk, of course, the higher immunological risk, the more potent the immunosuppression they need. And if they experienced a rejection, we intensify immunosuppression. If they experience infectious complications, we reduce the immunosuppression. If they experience a particular side effect that we know, that it's associated with a specific drug, we get rid of the drug, replace with other, or sometimes, we just have to reduce the dose. So that's how it's managed. Your [INAUDIBLE] transplant center, we're not just close their abdomen and send them out, we have to follow for a lifetime. And so we regular see them at the clinic, we do regular lab monitoring, as well.

So this is a brief snapshot of what agents we use. So for your purposes, you're interested in kidney transplant. Some of your patients may get pancreas, kidney combined. And also, we transplant HIV+ recipient. So there are slight differences, but I want to just notice here the first bullet all describe antibody induction that we give for a highly-- high immunological risk patients. The second bullet, those are the maintenance immunosuppressive agents, they continue. There are smaller set of patients may receive steroid avoidance in maintenance immunosuppression, because as you know, steroids has a lot of side effects. We hand picked those patients, because the lower immunosuppression, the higher risk of developing rejection. So only low immunological risk patients will qualify to receive a very short steroid immunosuppression after the transplant.

These are the commonly used immunosuppressive agents in the United States. You recognize in the left hand side, we use a steroid and we use Tacrolimus, most is a calcinating inhibitor, and we also use Mycophenolate, which is anti-proliferative. But you can see also, there are alternative agents in the same class, which means that the other agents can be used as an alternative, for side effect and so on. On the right hand side, on the top, we have m-TOR inhibitor, which is also maintenance immunosuppression, they can be used instead of calcium ihhibitor or anti-proliferative. And Belatacept is maintenance, but it is IV medication. And the last three all are antibodies. And there are used for either induction and treatment of rejection.

So this is a summary table. We have anti-thymocite globulin, lane or the brand name is Thymo globulin. And Alemtuzumab, brand name is Campet, and Basiliximab, brand name is Similac. All of them can be used as an induction agent at the time of transplant. But note that Similac, or Basliliximab is only for induction, the other two agents can also be used to treat rejection.

Because ATZ and Alemtuzumab work by depleting t-cells, they are considered more important. So those will be affected-- I'm sorry, ATZ will be effective in treating rejection, but Alemtuzumab and Basiliximab is only for induction agent. But the Alemtuzumab and ATZs work by depleting T-cells, they are more potent. Therefore, the risk of infection associated with these two agents would be higher. So we need to provide more infection prophylaxis regimine, and premedication as well, because when T-cells rise, they will raise a lot of cytokines and during the infusion the patient can have fever or hemodynamic unstability. So those are the things that are slight differences, but since these antibodies are done impatient rather than outpatient, so you may not have any hands on experience with using this agent.

And these are the classes of immunosuppressive agents that can be used as a maintenance. So this picture illustrates how the T-cell media rejection happens. So you need three signals. Signal number one is the antigen presented by antigen presenting cells. On the lower side, you have a Thiel lymphocytes that recognize that. Signal number 2 is, of course, stimulation factor, which is a target of Bella taseff, the IV medication that I was referring to. And with signal number one and signal number two, your T-cells will start making cytokines. Out of all the cytokines into look into is the most important one that binds to interleukin to receptor, and then your lymphocytes would be activated and proliferating. That's signal numbers three.

[INAUDIBLE] receptor is located not only on T cells, but also b-cells and plasma cells. So it would just activate whole spectrum of white blood cells. And then, those will impact the new kidney and then cause damage to the kidney. So we need to catch this [INAUDIBLE] and then stop this process with a more potent immunosuppression, so that the injury won't occur. So the take home message is our immune system is very redundant. So if you block signal number one, and your immune system will find another way to compensate, so you can not just use one drug to prevent rejection. You need two or three drugs, ideally from different mechanism of action. It doesn't make sense to use two drugs from the same mechanism. So that's what we try to do when we designed the immune system, immunosuppression.

So steroid. So it is hardcore agent for the maintenance immunosuppression. And it's been years since the first kidney transplant in the United States happened, in 1954. So it's been over 60 years we've been using it. We've learned a lot too minimize the side effect of a corticosteroid. So we start at high doses, and gradually reduce to the maintenance proteins of 5 milligram per day, as soon as possible. And then, sometimes we use IVs steroid to treat mild rejection. If it is severe and that, they will probably need a T-cell depleting antibody to treat.

So as you know, steroid can affect every organ in our body. Most of these side effects, fortunately, is associated with the high doses. And we decrease our steroid to 20 milligram on day four. So we are talking about many of these will happen in the first week. And once we're down to 20 or lower, hopefully, we may not. But as you know, the eye cataracts, and glaucoma, it doesn't necessarily, with high doses. So the horror stories about steroids that our kidney transplant patients are scared of, because they were on 60, 100 milligrams of prednezone on to treat their initial native kidney disease. But it is a little bit different approach.

Still, long term use will cause a lot of metabolic complications. Then, in turn, lead to increased cardiovascular risk. Cholesterol problems, hypertension, and sugar problems. It is still a problem, I'm not denying that. But about five to seven years ago, there was a very strong interest in the transplant community to get rid of steroids so that we can prevent this. So there have been well-designed prospective triers. Can we really get rid of steroids and prevent all these problems? Well, in the first year, yes. Definitely, they have a lower side effect, metabolic wise. But five year follow up showed they probably have about the same incidence of diabetes, compared to no steroids at all. But the key is we taper down your steroids to five milligram, if acceptable, from rejection risk standpoint. That will prevent the metabolic complications and minimize the risk, as well. But once we-- we usually decide which patient will get steroid avoidance on long term, based on their immunological risk, so the course doesn't change over time. So we already know which one will need long term steroids. So telling them there is a possibility you will be able to get off steroid, it's probably not true.

Calcineurin inhibitors, this is actually the most important agent out of the triple maintenance regimen we use. We use tacro microphelonolate, and prednezone for long term maintenance. And there are two agents. If you remember your transplant patient from 10, 20 years ago, they were on cyclosporine. So tacro, cyclosporine, they work the same way. But what we found, after tacrolimus has have been used in clinical kidney transplant patients, for more frequently, it is superior to cyclosporine. From rejection rate, from grave survival rate, and patient survival rate.

So if you look at the national data, about 90% of new kidney transplant patients in the United States, they are started on tacrolimus, that is how this one has a good track record. And recently, tacro, more, newer formulations of tacrolimus became available. Used to be immediate release every 12 hours apart, still 95% of tacrolimus in the market are immediate release, but slowly, the once daily extended release tacro is gaining traction, and over time, you may see that patients are on extended release.

They are not interchangeable pharmicokinetically, so we need to be very careful when we do the med reconciliation in the set round, so that we don't confuse, and accidentally give different formulation. Side effect of tacrolimus. So I told you that every single drug has their own side effects. And particularly, calcineurin inhibitors have concentration defendant nephrotoxicity. They are very effective preventing kidney transplant rejection, but when their level is high, it's going to injure their kidney. That is why we try to prevent. One of the primary mechanisms for chronic rejection is known to be due to the tacrolimus and nephrotoxcicity. Network You may recall that the transplant patient need cyclosporine level and tacrolimus level monitoring. This is why we need to do the regular schedule of the monitoring, to avoid a nephrotoxiciity, also to avoid under immunosuppression.

And other tacrolimus side effects are hypertension, neurotoxicity, as well. Because calcineurin inhibitors are vagal constrictors, so that is why you will see hypertension. And the different side effect between cyclosporine and tacro, tacro tend to cause a post-transplant diabetes, cyclosporine cause more cholesterol problem. Tacrolimus cause hair loss, cyclosporine cause hair growth. Cyclosporine causes zinjibar hyperplasia, but not tacro. So the blue represents different side effects, pink, there are common side effects between the two. But the major side effect is a concentration dependent nephrotoxicity.

These are not inclusive, but I wanted to show you what the common and major side effects of our patients can get from different agents that we use. So those are included for your reference. These two agents, mycophenolate and belatacept, they're under FDA REMS protocol. What that means is that there is probably not very common, but serious enough side effects, that FDA wants to monitor for a long time before it just really is for your use, without the restriction.

So the risks associated with mycophenolate is increased risk for miscarries and of fetal malformation. So we have to educate female patients in childbearing age and we need to counsel the patient on effective contraception, because pregnancy in transplant is a high risk pregnancy. And if they accidentally become pregnant while taking this medication, the risk of the malmformation is very high. Belatacept has been associated with increased risk of developing fatal CNS post-transplant lymphoproliferative disease, so FDA is keep an eye on it.

So I told you before that we need to monitor the levels of cyclosporine and tacro, and also the emptor inhibators, we monitor their levels regularly, because there is a very narrow therapeutic range that we want to target to avoid a rejection, also minimize the side effects. How we determine the target range? Depending on the center protocol.

And you heard that cyclosporine and tacrolimus have a lot of drug interactions, it's because they are substrate for CYP enzymes, which the metabolic enzyme that metabolizes a lot of other drugs. In fact, more than 50% of drugs marketed in the US are inhibitors or inducers and substrate of this enzyme. So there is a very high drug interaction potential with immunosuppressive agents. And also, each individual patient may have different activity over these enzyme. So even if thirty of us take tacrolimus, two milligram at the same time, our levels can be very, very different. So we start fix those, based on the weight, and then we monitor their levels, and we adjust our taxonomist stores based on that concentration that we measure.

So I mentioned about the drug interaction. So the examples on your left side, those are inhibitors of CYP enzymes, so therefore, if you use these drugs with the tacro, tacrolimus level will go up. Not all inhibitors are the same degree, so depending on how potent they are, we may need to reduce the dose of tacro when you add this agent. Or sometimes, we just need to keep an eye on the trough.

And right side, we have inducers, meaning that they will induce the enzyme, so more metabolism and you expect that tacro level will go down. And notice not only the drugs , but some fruit can inhibit the enzymes, as well. And you all know grapefruit is enemy, right? But now we have learned pomegranate, papaya, and pomelo. Pomelo, it's a citrus fruit, looks like a grapefruit, but it's lime color. So all of these also moderate inhibitors of [INAUDIBLE] enzymes. So not only you here that grapefruit is a no-no from now, but pomegranate and the other fruits as well. They often ask me, pineapple, mango, those are OK. Because we don't have human data that it would cause a clinically significant interaction. And because of the tacrolimus nephrotoxicity, we try to avoid other nephrotoxic drugs, if possible. NSAIDs, contraindicated. Never, never, never.

AUDIENCE: That does not include Tylenol, correct?

JAMIE PARK: Yeah, Tylenol is a safe drug, because it's not NSAIDs. And then aminoclycosides, IV contrasts, we try not to use unless it's absolutely needed. So I cannot emphasize enough how important it is to take medication as it's scheduled for our transplant patients. So initially, they were very adherent to their medication regimen, but as you know, Medicare covers immunosuppression only these three years, right? So either financial reasons or they just went back to their normal life, the life in the way, and it's busy, they forget, and are they feel good, so that they don't feel like they need to take medication, so they become slacking. And medication adherence is number one reason for late rejection. And this late onset resection is typically chronic in nature, the damage is usually irreversible when we find. So this is one of the reasons why people lose their organs. So it's important that we keep in touch with the patients, even though they are three, four years out of transplant.

Initially, we educate them about this, but over time, they forget things. And the last [INAUDIBLE] is really, really important. It is impossible to provide what prescription and what over-the-counter drug, what other supplements they need to avoid. So every time they're thinking of starting something, or get a new prescription from their PCP, we ask them to contact the transplant team. So that is why we want to send this out, a program like this one, so that you guys can involve and reinforce and remind the patients how it is to-- how important it is to have a long standing, regular follow up with the transplant team.

So hopefully, today's program, you've learned that it takes a whole village to take care of kidney transplant patients. So that's why we do it every day. Thank you.

[APPLAUSE]

Questions?

[ON SCREEN QUESTION SUMMARY]

AUDIENCE: Because of the [INAUDIBLE], should the liver enzymes be watched more carefully or more often?

JAMIE PARK: So the main metabolic enzyme that is involved in drug metabolism, it's a CYP3A4. Fortunately, this one has very wide capacity. So unless you're more than half of your liver becomes [INAUDIBLE], it really doesn't affect liver enzymes itself. So that's very fortunate. But of course, liver transplant, we monitor liver enzymes to monitor liver function, but not necessarily for the drug toxicity. Any other-- yeah?

AUDIENCE: What's the typical cost for transplant patients a year for medications?

JAMIE PARK: Oh, with insurance, without insurance?

AUDIENCE: Without insurance.

JAMIE PARK: Without insurance, I must say it's probably close to $1,000 per month. Yeah, more than that. Especially when you're on in the beginning, that infection prophylaxis. One of the antiviral agents we use is a very aciclovir that happen to be a most expensive drug, out of pocket cost, it is usually $800 per month. So yeah, it's expensive. So it is important that they recover from the surgery. If they are able to work, and it's important they maintain good insurance and coverage.

And I'm not trying to be political here, but if there is any we-- couple of years ago, we submitted a bill to become lifetime coverage for immunosuppression, but it didn't get approved. So if you hear that there is a public hearing or supporters, I encourage you to think about your patient, so that we can get lifetime immunosuppression coverage from the government.

AUDIENCE: It used to be that, on of the nephrologists that I worked with said, oh, transplant has followed them for a couple of years, but then they sent them back to me. Is that true, still?

JAMIE PARK: Yeah.

AUDIENCE: And the regular nephrologist is able to attack and monitor this, as well, for the transplant change?

JAMIE PARK: So there are different pathways. Some on the general nephrologists have taken care of transplant patients enough, so they are going to manage the immunosuppression levels. But most of our patients, even though they go back to their local doctor for monitoring, they are doing function and blood pressure management, etc, but we still get their labs faxed to us, and we are-- a lot of our patients are still-- our transplant nephrologists are adjusting their immunosuppression levels.

SPEAKER: They come to see us once a year, and at six months, if they're doing well, they go back to their nephrologist, but keep seeing us once a year.

AUDIENCE: Until-- for how many years?

SPEAKER: Forever.

JAMIE PARK: Forever.

SPEAKER: So they go back to their general nephrologist to see regularly, but then they see us once a year.

JAMIE PARK: Yeah, in the past, we managed all of aspect of their health care, but now we try to move, transition the management of chronic disease to PCP or local nephrologists but we own the immunosuppression. Yes.

AUDIENCE: So if our patients can move around [INAUDIBLE].

JAMIE PARK: Yeah, our patients move to Florida, California, so we have nephrologists to neph-- or transplant center to transplant center to transition their care smoothly.