

[MUSIC PLAYING]

**RAJIL MEHTA:** Immunosuppression is a little bit of a dry topic but it's very important to understand the basics. A lot has changed over the last several years. So please feel free to ask any questions. So 30 minutes is quite short to go over you know most of the aspects of immunosuppression.

So what I wanted to really do is just go to the major successes that we've had over the last 50 years or so and also look at some of the challenges that we face today. We'll talk a little bit about induction therapy and maintenance therapy, and a little bit about where we are headed down the road. This is not a very pretty slide I admit. But it's very important because it kind of conveys to you where all the immunosuppressive agents act and why we use what we use.

So over here on the left, you'll see some of the calcineurin inhibitors. And then you'll also see some of the induction agents that we use, such as basiliximab, and then the cell cycle that's affected by the mTOR inhibitors and also the anti-metabolites. So it gives a nice overview as to the different targets of action of the immunosuppressive agents that are being used today.

And this is very nicely explained with the three signal hypothesis, the first signal being the presentation of the antigen to the T-cell. The second thing that needs to happen is the binding of co-stimulatory molecule, which gives a signal, too. And that subsequently leads to release of interleukin-2, and then subsequent proliferation of the T-cells.

Let's talk a little bit about the induction therapy. The purpose of induction therapy, essentially, is to prevent early acute rejection. Although, historically-- today it's not as important because the maintenance immunosuppression is very important. What is also seen now is that the-- because of the evolution of the cross match techniques and better DSA techniques, we don't quite have as many immunological issues that we face today. And the potent maintenance therapy, as we'll talk about shortly, is also pretty important in decreasing the rates of rejection today.

So, broadly, this T-cell depleting therapy, which we use for the most part, and that comprises of thymoglobulin-- and there's also non-T-cell depleting therapy, which comprises of the interleukin-2 antagonists, such as basiliximab, which also we use from time to time. We did use Campath a lot in the past-- not anymore.

Just a brief overview of the induction agents-- so basiliximab, as you may be aware, it essentially acts on the interleukin-2 receptor. And it's very easy to administer two doses, and you're done. Daclizumab is no longer available.

Then we used rabbit anti-thymoglobulin, which is essentially prepared by injection of human thymocytes into rabbits. And these preparations are batched, and then this is what we administer as induction therapy for most of our patients. There was a similar preparation obtained from horses called ATGAM, which we don't use anymore. And then we have alemtuzumab, which is still being used in some centers. And then OKT3, which, again, we do not use anymore.

If you look at the trends in the induction agents over time, essentially, it's hard to decipher all the various therapies. But the one thing that stands out is that the use of thymoglobulin has gone up quite a bit over the course of the last 15 to 20 years. All the other agents are either stable or the use has declined over time.

Again, here, the use of the induction agents have basically-- this shows the alemtuzumab thymoglobulin interleukin-2 receptors. And what stands out here is that the rates of acute rejection have gone down, even in cases where there's no induction. So what does that tell you? It basically tells you that the potent immunosuppressive maintenance therapy is very effective today.

There are many challenges that we have in induction therapy. We don't really know the impact of induction therapy now on the long term graft class. And there are really no randomized controlled trials that have compared the different agents.

Let's talk a bit about maintenance therapy. Essentially, everyone here is familiar with calcineurin inhibitors. That's the mainstay of our therapy. There's also anti-metabolites, which includes mycophenolic acid. And then we have mTOR inhibitors, which I won't go into much, steroids, of course, and then belatacept.

So the discovery of cyclosporine in the early 70s really made a big impact on the rates of rejection and the outcomes that we see today. Over the last 50 years, essentially, though, it is to be noted that calcineurin inhibitors still are the mainstay of therapy.

This was initially investigated as an anti-fungal agent-- that is, cyclosporine. They really didn't find it of any use as an anti-fungal agent, but it had some immunosuppressive properties. And that's how we ended up using this today. Tacrolimus came in the mid-'80s, and the clinical studies started here in Pittsburgh in the late '80s. And till today, it remains the cornerstone of maintenance immunosuppression.

Now these two are actually structurally very different, but both cyclosporine and tacrolimus, they bind to their targets. And both of these, essentially, will act on the calcineurin, which is responsible for stimulation of the interleukin-2.

This is a very nice slide, because it conveys a lot of important developments over the course of the last 50 years. As you can see here, in the '80s, with the introduction of cyclosporine, the line in black there essentially shows the decreasing rates of acute rejection. And concomitant with that, you can see the improved one graft-- one year allograft outcomes, which improved quite a lot over the past 50 years. And then, again, with the introduction tacrolimus and introduction of MMF, the rates of rejection have decreased even further.

And so once calcineurin inhibitors came into play, we've had several studies which have compared tacrolimus with cyclosporine. And there have been several different preparations of cyclosporine. In general though, for acute rejection, tacrolimus has been shown to be superior.

There was also another study comparing tacrolimus with the other agents, such as cyclosporine, as well sirolimus. And again here, the rates of acute rejection that are seen with tacrolimus are much lower than those seen with the other agents, including cyclosporine and sirolimus. Additionally, the graft survival was also noted to be better.

This was the elite study, which was published about 10 years ago. It does have some major drawbacks, including the low percentage of African-American patients in this study. But nevertheless, it remains an important study to date.

We're all aware of the major adverse effects of cyanide, nephrotoxicity being the major one. We do see some neurotoxic issues with some of our patients on tacrolimus, some issues with hirsutism for those on cyclosporine, and then some issues with hypertension, hyperlipidemia, and post-transplant diabetes.

Can we really get rid of nephrotoxic effects of these agents? This was a study which tried to address calcineurin inhibitors to see if the kidney function would be better. You do need to have very nice acronyms for these studies in order for them to be successful. So this was the CAESAR study, essentially a prospective randomized study which split the patients into a cyclosporine withdrawal group, and then low dose cyclosporine and standard dose cyclosporine.

Essentially, what they saw is that the rates of acute rejection at 12 months were pretty high in patients who were withdrawn off the calcineurin inhibitors. Also, the expected benefit in the improvement of GFR was not really seen with the calcineurin inhibitor withdrawal.

I just want to mention about tacrolimus LTP, or the long acting tacrolimus preparation. It's an extended release preparation. It's given once today. The bioavailability is much better-- about 30% lower doses of tacrolimus are required. And the fluctuations in the peak to trough of the tacrolimus is much less in this agent. We do use this in some of our patients, especially those who require very high doses of tacrolimus, including some African-American patients.

So to summarize CNIs in renal transplantation, can't really do with them, can't really do without them, though. What about the second agent? So CellCept has been around for a long time, and it's analog, myfortic, or mycophenolic acid. And before the 1980s, azathioprine was widely used. And so, obviously, there have been several studies which have compared MMF with azathioprine.

In general, it's, again, somewhat of a gray area. But I'll just show you one randomized study, which compared the rates of acute rejection. And, of course, these are concomitantly used with calcineurin inhibitors. And this is a Forest plot which shows the outcomes, here. And, as you can see on the left side, there did seem to be some benefit to use of mycophenolid as opposed to azathioprine in decreasing the rates of acute rejection.

Similarly, with graft plots, there seemed to be a minor benefit with use of mycophenolid. And so this, along with tacrolimus, remains a mainstay of therapy today.

What about belatacept? As I mentioned earlier, a co-stimulatory signal is necessary for activation of the T-cell. After presentation of the antigen by the antigen presenting cell, there's another step that needs to take place. And that's the co-stimulatory pathway.

Belatacept is an agent which blocks this pathway and essentially stops the proliferation of the T-cell because of blockade of the co-stimulatory pathway.

This was one of the first phase two trials that came off with belatacept. It was a rather large phase two trial with many centers. And, essentially, they compared belatacept with cyclosporine. The primary endpoint was non-inferiority of the belatacept as compared to cyclosporine. And the rates of acute rejection, essentially, were not found to be different in the three groups.

Three year outcomes were published in 2012. And, bottom line is that the GFRs at the end of three years were almost 20 mL per minute better with the belatacept group as opposed to the calcineurin group-- the cyclosporine, rather.

One thing that they did notice was that the rate of rejection was higher in the belatacept group. But that did not make a difference in the GFR at three years. One of the main drawbacks and critiques of the benefits study is that they did not compare belatacept with tacrolimus, which is the main agent that's used today.

There was a publication about two years ago that compared the long term outcomes-- that is seven years of follow up in the same cohort of patients. Again, the main GFR was higher in the belatacept-treated groups. And patient and graft survival was noted to be better.

As of now, belatacept is extensively used in some programs. Our program uses it selectively for patients who are intolerable to calcineurin inhibitors or those who have unexplained poor renal function.

I also wanted to mention a little bit about the future of immunosuppression. It's pretty clear that, with all the long term nephrotoxicity of CNIs and the potential for malignancies and infections, there are other therapies that are being looked into. There are a whole range of therapies that are being looked into.

I just wanted to briefly mention about the T-cell therapies. As you're aware, the T-cell can differentiate into a few different subsets of cells. One of these is the T regulatory cell, which uses FOXP3 as the transcription factor. And essentially, this is responsible for decreasing or suppressing an immune response.

The idea here is to, through leukaphoresis, isolate the T regulatory cells, expand them ex vivo, and then reinfuse the T-cells into the patient to suppress any immune response or suppress rejections, basically. This is still in trials. There are a lot of logistic difficulties here. How do you isolate the cells? How many cells to use? A lot of this data is extrapolated from mouse data. Whether the cells will remain in circulation, what concomitant immunosuppressives to use-- a lot of things being sorted out right now. But this has been successfully used in some trials with type 1 diabetes, as well as graft versus host disease, as well as liver transplantation. And more recently, a phase one trial in kidney transplantation has also used this for very minor levels of inflammation-- what we would call subclinical inflammation.

So to conclude, thymoglobulin remains the most widely used induction agent today. Almost 60% of the programs use it. Simulect used in approximately 20%. Tacrolimus with MMF remains the mainstay of therapy with or without steroids. Cyclosporine has been substituted in some cases, for various reasons. Belatacept with them MMF and steroid also is being used on some of the patients. There are a few special circumstances where an mTOR inhibitor such as rapamycin or everolimus has been substituted. For instance, patients who are having recurring skin cancers or those with CMV infections.

One of the biggest challenges we face today is that the long term outcomes have not really improved the way the short term outcomes have improved in kidney transplantation. And there's no clear-cut explanation as to why that is. I recently came across a very interesting study that compared the long term allograft outcomes here in the United States with Europe, and also with Australia.

And here, what you can see is that the one year outcomes are excellent for patients here in the United States. But if you extrapolate that long term, the 25 year, or the long term outcomes, are lower, even when we compare them to other continents. And there are a few different reasons. We may be doing more complicated, more comorbid patients. Or whether it has to do with the change in insurance coverage after three years, we really don't know. But I think, before we embark upon any major newfangled expensive therapies, it would be reasonable to look at some of these and try to see if there are any causes which we can rectify right now to improve the long term outcomes.