[MUSIC PLAYING]

RAJIL MEHTA: And I'll be talking, you know, about the Banff classification, mostly on its updates and also some of the updates in subclinical and in antibody-mediated rejection. So I would encourage you to ask any question, because I know that not everyone is familiar with all the classifications of Banff. So feel free to pop in any questions if you have any queries. All right.

So in terms of subclinical rejection, we'll be mostly talking a little bit about T-cell-mediated rejection, which is the bulk of what we see. We hardly see any subclinical antibody-mediated rejection here since we don't transplant across the HLA and ABO barrier. No financial disclosures.

Discontent is the first necessity of progress. And I think it's this discontent that led to the improvement in the one-year allograft survival. If we were having this discussion in 1980, I would have left all my toys and come for this discussion to discuss about improving the one-year graft survival.

As you can see, in the '70s, the rate of acute rejection during the first year was 50% to 60%, and the graft survival at that time was also around 50% to 60%. And so there has been a significant improvement now with acute rejection rates being less than 10% at one-year. So what that means is that the whole focus now, in all these updates and in all the new medications that come out, they have to be focused on long-term outcomes and not on short-term outcomes.

So the black line here, you can see the dramatic decrease with the introduction of calcium neuron inhibitors. And with the red line there, of course, represents the one-year allograft survival. You would think that this would translate to an equivalent improvement in long-term allograft survival, but somehow it does not. However, there is some hope.

If you look at the five-year survival, in the year 2000, it was about 20%, I should say, graft failure. That [INAUDIBLE] graft failure was around 20% in 2000. It's closer to 10% now, which means that about 20 of the 100 grafts would fail in 2000, but about 10 out of every 100 grafts are failing now. So there is continued improvement in the overall allograft survival.

So we'll start with the Banff updates. As you know, Banff is a resort town in Canada, and it's known for its hot springs. And actually the name Banff came from a town in Scotland, where the president of the Canadian railway was born, and it was named after that. But anyway, it was here that a group of pathologists, transplant surgeons, and nephrologists met in August of 1991 and had the first Banff session.

And since then, there have been periodic updates every two years, so it's a very dynamic classification. The next one is actually going to be in Pittsburgh in September.

Take a look at this slide. This is the first Banff classification. Interestingly, you will see here acute rejection listed. There has been dramatic change over the last several years, and actually this would span a quarter century now, with regard to the developments in HLA technology and also the clinical developments. And we'll just briefly go through some of these updates.

Now for those who are not familiar with this, the first one refers to acute rejection here. Then you have the borderline categories, and then the T-cell-mediated rejection, and then the chronic allograft nephropathy scores. This paper, almost exactly 50 years ago, changed quite dramatically the way we look at preformed antibody. This was a seminal paper in IgM by Patel and Terasaki, where essentially the idea is very simple.

This was a multi-center study. Those were the positive cross match. Out of the 30 patients who had a positive crossmatch, 24 of them had rejection. And out of the 195 patients who had a negative crossmatch, only eight of them had rejection.

So then we don't need a chi-squared calculation here, right? So you can tell that this is very significant. And so this was the initial CDC crossmatch, and over the years, now we do the flow crossmatch. And with all these, the rates of hyper acute rejection dramatically decreased over the next several years.

What they did start noticing, though, was some kind of rejection that was associated with HLA antibody, and also was associated with peritubular capillaritis, and also glomerular inflammation. And that was quite different from the garden variety T-cell-mediated rejection that they were seeing, which was missed mostly confined to the tubules and the interstitium.

So on the left here, you can see the glomerulus with inflammation, and the right side figure mostly shows a peritubular capillary with inflammation. And so this was characterized as antibody-mediated rejection, and for the first time, in 1997, that was introduced into the Banff update.

So essentially, there were three main categories, or three main features, that were needed for diagnosis. One was microvascular inflammation, which is peritubular capillaritis as well as glomerulitis. And the association with HLA antibody. And then there was the C4d deposition in peritubular capillaries. And C4d is essentially a stain that is a telltale sign of complement activation, which is very much necessary for antibody-mediated rejection.

So this was the Banff 2005 update, where they just had some different phenotypes of antibody-mediated rejection, but notice that all of them have C4d required for diagnosis. And then there were a few studies that came out from the Edmonton group and also from the Paris group that noticed that antibody-mediated-rejection-like damage was also noted in patients who did not have Cd4 staining.

So that led to the most important update here in 2013, where they removed C4d as an absolute requirement for diagnosis of ABMR, and it was partly replaced by the-- you could have genetic transcripts that were suggestive of antibody-mediated endothelial damage. And that could basically replace the C4d positivity. And then more recently in 2017 with the advances in HLA technology, even the DSA can potentially be replaced if you're able to test for non-HLA DSA or do molecular testing.

All right. In terms of borderline rejection, I just wanted to mention one thing. The requirement for the level of inflammation was downgraded in 2005 from A1 to A0. A1 essentially refers to 10% of interstitial inflammation in the cortex. No major significance of this in terms of therapeutic strategy though.

The one other interesting update that was part of the 2017 update is the introduction of i-IFTA. For a long time, which has been known and noticed that inflammation in areas of IFTA or Fibrosis and Tubular Atrophy, those allografts are a much worse prognosis. So prognostically based on a few studies from Loupy's group in Paris and also from [INAUDIBLE] group in Australia, they came up with the i-IFTA addition, and this is part of the chronic active TCMR addendum that was made.

So where are we going from here? One thing seems definite. There's only so much we can do with histology. At some point, we would have to introduce some kind of molecular testing to confirm diagnosis of either TCMR or ABMR. And so for instance with borderline infiltrates, we see this all the time. We don't know if it's going to progress to TCMR or not.

And so some form of testing with genetic transcripts would really be of value, and that's really being done in several centers now. At least, the studies are ongoing. Nothing in the clinical arena yet, but I think we'll see something soon.

Moving to subclinical rejection, this basically represent histological features of acute rejection in the absence of an actual decline in renal function, and it is, of course, only diagnosed in surveillance biopsies. Most studies use a threshold of 10% to 25% of change from the baseline renal function.

Now before I came to UPMC, I could only see the tip of the iceberg. That was my view of TCMR, because I was only at institutions we did not do protocol biopsies. Now it is easy to see that there is a lot of subclinical rejection, and this goes way beyond what we diagnose as clinically-mediated T-cell-mediated rejection.

We tried to understand this better when we reviewed all the studies and subclinical rejection. And as you can see on the top there, the study by Rush and his colleagues from Manitoba reported 30% at three months. This is, of course, an old study. And then if you see down here, Heilman and his group from the Mayo Clinic in Arizona at a prevalence of 7.4% in one month.

There is a lot of discrepancy. Our own prevalence here is somewhere in the range of 15% at three months. And we understand now that this difference in prevalence is because of the differences in induction therapy, and the differences in the maintenance therapy, and also difference in the timing of the biopsy.

One of the first studies to point out the importance of subclinical rejection was done by Rush and his colleagues from Manitoba. And here, treated patients with subclinical rejection had better renal function at two years, as compared to those who were not treated. And also, the chronicity scores in these patients were much better as well. The problem is that we don't really have any good long-term data with subclinical rejection.

This is one of the studies that was published several years ago. It's a Korean study. It had about 300 patients. They all underwent a biopsy at two weeks, and they were hollowed out for 10 years. And those who had subclinical rejection had the worst outcomes. The ones with normal findings and those with borderline rejection had almost equivalent outcomes.

We also tried to get a better idea, of the practices across the country, about who's doing protocol biopsies and who's not. We sent out a survey to about 275 centers. We got a response of around 45%, which isn't too bad. And essentially, the findings are pretty interesting.

Number one, more than 60% of the centers don't do protocol biopsies across the country. Only 17% did protocol biopsies in all their patients, and another 21% didn't select patients such as those who are transplanted across the ABO barrier or the HLA barrier. And there are many reasons why centers don't do protocol biopsies.

Almost 40% believe that doing protocol biopsies will not change the eventual long-term outcome. About 32% reported that they had staffing issues, and about 18% said they had insurance issues for which they could not pursue protocol biopsies.

There was a similar study done in Canada, where they surveyed the 25 Canadian centers and got a response from 18 centers. And fairly similar results, I would say. They had 28% of centers that did protocol biopsies.

With regard to the treatment practices in our study here, out of the 54 centers that performed protocol biopsies, 47 of them were treated with either steroids, or adjustment of immunosuppression, or thymoglobulin, or plasmapheresis IVIG if there was suspicion for ABMR. If you look at the Canadian findings, they're pretty similar. 91% of the centers would greet the subclinical rejection.

Although it makes me wonder why then 9% would not do anything. There's no point in doing a biopsy. They're not going to do anything about it.

We also have known for a while though that steroids may not necessarily be the answer. Despite treatment, we find a lot of persistent rejection in our patients, and this has been reported before. And more recently when they were testing biomarker for subclinical rejection, they reported their data on follow-up biopsies, and essentially over 50% of these had persistent inflammation. So it tells you that steroids may not be the only answer or may not be efficacious in treating this condition fully.

So the question is, are there any other therapies that we can use? Dr. Sood talked about anti-IL-6 therapy that's being tried in chronic ABMR with some results. We don't have any current results reported yet from the subclinical rejection trials.

With regard to T-regulatory cell therapy, this is an interesting way to harness one's own immune system. The T-cell differentiates into several different effector cell types, and one of the other cell types that it differentiates into is called the T-regulatory cell. And this is primarily responsible for induction of immune tolerance and also to tone down, or to regulate, immune responses.

And so many centers are using T-regulatory cell therapy both in liver as well as kidney transplantation to see if we can wean the immunosuppressive agents down. And this just lists a bunch of centers using this therapy.

Now we are participating in the task trial which is one of the centers, and essentially, there is three arms to this trial. There's a standard of care arm, and then there are two arms where the patients receive T-regulatory cells for subclinical inflammation on the biopsy. This level of inflammation is even lower than subclinical rejection.

But essentially, the other two groups would undergo leukapheresis, and the T-regulatory cells would be expanded ex vivo and then reinfused. The only difference between group two and group three is that, group three, the patients with the T-regulatory cells would also be exposed to the donor antigen. These are all from live donor transplants.

The biggest problem. Actually two. Number one, it requires an additional biopsy. So in addition to the three-month then the one-year protocol biopsy, we would need to do an additional biopsy after the infusion of T-regs, and of course, patients are petrified of biopsies.

And the other thing is that we don't really know how efficacious the therapy is, so we can't really give that assurance that this is going to take care of it all. So these are the two main reasons. And so we started enrolling patients in October of last year. So far we have not enrolled a single patient, but there are about eight centers currently in the trial.

Also keep in mind there are a lot of things we don't know about this therapy. For instance, we don't really know what is the exact correct those two use of the T-regulatory cells. We don't know how long they will last in circulation. What would be the best maintenance immunosuppression to use? Whether we should use mTOR inhibitors or whether we should use CNIs with these?

As far as updates and antibody-mediated rejection, as I mentioned antibody-mediated rejection was first introduced in 1997 into the Banff classification. And over the last several years, the HLA technology has taken off quite a bit, and along with that, there have been a few different therapeutic agents that have been used for ABMR. So we'll just briefly cover some of these.

You could potentially target ABMR at several different sites, and these are the sites that have been used for targeting with newer therapeutic agents. You could use, well, steroids, thymoglobulin to attack the T-cell or to decrease the T-cell/B-cell interaction. Or at the level of the B-cell, rituximab has been tried, and we'll look at some of the trials there.

Bortezombi, as you know, is being tried in some centers. We've used it on a minority of patients not with great results so far. And of course, plasmapheresis. We could just take the antibody out. Or IVIG to decrease the efficacy of the antibodies that are there. Or lastly, use of complement therapy such as eculizumba or the C1 esterase inhibitor, which Dr. Sood talked about in the morning.

Now the problem is-- so this was a recent metaanalysis that was done looking at all these different therapies. The biggest issue is that all the study quality, based on the great criteria, essentially, they're all low quality to moderate in quality in terms of the study design. Most of these are single-center studies. Some of them use historical control groups. So the answer is a little difficult.

Let's look at some of these with regard to antibody removal, for instance. This is a forest plot. The side on the left here would represent favoring of antibody removal. The one on the right would favor control. And as you can see, the diamond there crosses the line and essentially tells you that this did not reveal any statistically significant benefit in using antibody removal in ABMR.

What about antibody removal and IVIG? There were two retrospective studies here, and one of the two showed a benefit for plasmapheresis with IVIG in a seven-year follow-up. Now having said that, this still has become the standard of care today.

What about rituximab? We have used rituximab in the past, and there are still some centers using it. There were two non-randomized controlled trials in the past which used historical groups with no definitive results and then two RCTs, and I'll just mention about one of them, which is the Ritux era. And this was a multi-center double-randomized trial, which basically had rituximab added to the standard of care, which was plasmapheresis, IVIG, and corticosteroids.

And the other arm which are, again, 19 patients had placebo with the standard of care. And they did not find a difference in their primary outcome, which was graft loss, or a lack of improvement in the creatinine at day 12. Although this trial failed, it did further emphasize that plasmapheresis with IVIG was pretty efficient because the one-year graft failure rate here in this trial was only 5%.

This was another trial that was recently published. The BORTEJECT trial, and essentially, this was for late ABMR. And we have, of course, 21 patients here in one arm and 23 in the other arm. No difference in the slope of the GFR. This was a linear-mixed model we just followed over time. As you can see, the two lines are pretty similar, and no difference in the drop in the GFR over time. No difference in that center graft survival, or overall graft survival, or patient survival.

Lastly, coming to the complement system, we have a terminal complement inhibitor, which is eculizumab, and then C1 esterase inhibitor which attacks the proximal aspect of the complement cascade. And there was one study with the C1 esterase inhibitor, which was a double-blind placebo-controlled pilot trial. This was published in AGT by Montgomery and his colleagues.

Nine patients in each arm. A standard of care in both arm, plus C1 esterase inhibitor in the treatment arm. No difference in primary outcome. The six-month biopsy did show slightly less transplant glomerulopathy in the C1 esterase inhibitor group.

What about eculizumab? This was tried for chronic antibody-mediated injury, the pilot randomized-controlled trial. Small number of patients randomized-- one is to 2. 10 patients received eculizumab for six months with six-month follow-up. Essentially over time, no significant difference in the change in GFR. And of course, you know that you would probably pay a half a million dollars for a year of eculizumab therapy, so the significance should be really, really good if you're planning to use this one.

And one last thing, Dr. Sood did allude in the morning to [INAUDIBLE] therapy, so I'm not going to go over it too much. Essentially, this is pretty novel, though very interesting. IgG-degrading enzyme derived from a bacterium, which essentially would cleave the IgG molecule at the hinge region and render it incapable of attaching either to complement or to the antigens. Very efficacious in terms of decreasing the DSA titers, pre and post you can see there.

This study was carried out in Sweden and United States with a total of 25 patients. And just one note here. So 80% of these patients had a positive crossmatch. Results were excellent. [INAUDIBLE] removed or reduced DSA. In 24 out of the 25 patients, only one graft loss. The problem is we don't really know what the long-term outcomes are. And the other thing is that the enzyme itself is immunogenic, so you probably may not be able to use more than a couple of doses because they will develop antibodies. So it would be pretty inefficacious after that.

So in conclusion, the Banff updates reflect the evolution of clinical and technological advances in transplantation. The long-term impact of subclinical rejection and borderline rejection still needs to be evaluated. Alternate therapies are needed for TCMR and also, I would say, for ABMR, but plasmapheresis and IVIG remain the standard of care currently despite the poor quality of the studies so far. Thank you.

[APPLAUSE]