Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/clinical-practice/nephrology/is-there-still-any-role-for-plasma-exchange-in-aav/14174/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Is There Still Any Role for Plasma Exchange in AAV?

Announcer:
Welcome to this episode of KDIGO Conversations in Nephrology. This episode, titled Is There Still Any Role for Plasma Exchange in AAV is provided by KDIGO and supported by Amgen. Here's your host, Dr. Vladmir Tesar.

Dr. Tesar:
Hello and welcome to KDIGO Conversations in Nephrology. I am Dr. Vladimir Tesar, Head of Nephrology at General University Hospital in Prague. And joining me to discuss the role of plasma exchange in ANCA-associated vasculitis is Dr. Michael Walsh. Michael is a nephrologist at St. Joseph Healthcare Hamilton and an Associate Professor in the Departments of Medicine and Health Research Methods, Evidence, and Impact at McMaster University in Hamilton, Canada. His research interests include the treatment of ANCA-associated vasculitis, cardiovascular complications of chronic kidney disease, and symptoms of chronic kidney disease. He was also the main investigator on the recently published PEXIVAS trial, the largest ever randomized control trial in ANCA-associated vasculitis which studied the role of plasma exchange as add-on treatment in patients with severe renal ANCA-associated vasculitis. Michael, welcome to the program.

Dr. Walsh:
Thank you so much, Vladimir, and also to the KDIGO organizers for putting on this series. It's a real pleasure to be here.

Dr. Tesar:
Thank you very much. So, let's begin our discussion with the first question. PEXIVAS study suggested there was no benefit of using plasma exchange in patients with ANCA-associated vasculitis and kidney disease or alveolar hemorrhage. Despite that, the KDIGO guidelines still suggest to use plasma exchange in patients with serum creatinine over 500 micromoles per liter. How do you reconcile this apparent discordance?

Dr. Walsh:
That's a great question, Vladimir. Just to clarify, PEXIVAS was designed to try and demonstrate whether or not there was a benefit of plasma exchange on a composite outcome of all-cause mortality or end-stage kidney disease. And we didn't show a benefit in this composite outcome in these patients who had severe ANCA-associated vasculitis, which we characterized as either reduced kidney function or diffuse alveolar hemorrhage.

There's an important point to remember though, in that the primary outcome, and the outcome upon which we based our statistical power was a composite. We used this composite of death and kidney failure because they're both very important to patients and clinicians. And they're both highly correlated with one another and similarly common in patients with severe ANCA-associated vasculitis. And really importantly, we believed that the treatment would have a similar effect on both death and kidney failure, given long enough follow-up. That's to say that we thought the effects of plasma exchange on kidney function would translate to a survival advantage later on.

What we found though, when we first of all did PEXIVAS, and then combined the PEXIVAS data with other randomized trial data that examined the role of plasma exchange in ANCA-associated vasculitis that we published in the BMJ earlier this year, was that the beneficial effects on kidney failure was present, but there was no, or maybe only a trivial effect, on death. Furthermore, the effects on kidney failure appeared to wane over time. We could see it at one year, but we couldn't really see it anymore by the time an average of three years follow-up had passed. Because of those issues, PEXIVAS was actually very underpowered to find this particular benefit of the effects of plasma exchange on kidney function alone. And that's maybe why it's not so surprising in retrospect that the results were neutral.

The metaanalysis, on the other hand, found a fairly large or at least moderate effect of plasma exchange on kidney failure. It also identified that there was a harmful effect in terms of an increased risk of infection that we hadn't anticipated.

So I think plasma exchange does still have a role, but it needs to be very carefully considered. The patients most likely to derive benefit are those who are at high risk of kidney failure, but a low risk of infection. KDIGO guidelines do suggest the plasma exchange in patients at very high risk of kidney failure defined by being on dialysis or at least a creatinine of over 500 micromole per liter. And there are some other patients that are likely to benefit, or at least that they may want the risk reduction in term - in terms of kidney failure, and the potential benefits of plasma exchange, and are willing to undergo plasma exchange despite the possible risks of severe kidney failure or severe infection. But those need to probably be discussed with patients individually.

Dr. Tesar:
Thank you very much for this explanation.

And my second question concerns renal biopsy. So how does a renal biopsy help select patients that might benefit from plasma exchange?

Dr. Walsh:
Thanks, Vladimir. I think this has been a bit of a hot topic since PEXIVAS. We didn't require the use of a renal biopsy for patients to enter PEXIVAS. The nephrologists instinctively know that renal biopsies help us understand the prognosis of patients with kidney disease. And a lot of that prognostic information really comes from the degree of global sclerosis and interstitial fibrosis seen on the biopsy. As such, you might expect that patients with really advanced fibrosis who are very likely to develop kidney failure, but they may also be unlikely to respond to treatment, the so-called point of no return. For those patients, plasma exchange or any other effective treatment to reduce the risk of kidney failure may actually offer no benefits, and may still expose them to the risks of the therapy just because they're so fibrosed that they have no possibility of return of kidney function or dialysis independence.

Having said that, there really isn't a lot of empiric data to define how much fibrosis or sclerosis creates the point of no return. In fact, in ANCA-associated vasculitis, even patients defined as having the most advanced fibrosis still have a chance of recovery. And even when we incorporate biopsy information into prediction scores, like the one proposed by Dr. Brix, one cannot quite define a patient with a really, really high chance of kidney failure. And it does not determine whether or not there's actually a change in the protection offered by plasma exchange.

So how do we incorporate it in the end? I think we need to try and use an overall estimation of the prognosis for kidney failure. And there may be some patients in which we get a better sense that there - may have passed the point of no return, and it's not useful to offer therapies like PLEX, because they also increase the risk of harmful side effects. That's about as accurate an answer as I think we can get at this time. There's more research required really to help define this.

Dr. Tesar:
Many thanks.

For those just tuning in, you are listening to KDIGO Conversations in Nephrology, and our today's topic is, Is There Any Role for Plasma Exchange in ANCA-Associated Vasculitis? I am Dr. Vladimir Tesar, and I'm speaking with Dr. Michael Walsh.

Now, as I understand it, Michael, there is also a limited place for plasma exchange in patients with ANCA-associated vasculitis and alveolar hemorrhage. So my third question is, do you perform plasma exchange in all patients with alveolar hemorrhage?

Dr. Walsh:
That's a great question, Vladimir. And I can say quickly, no, I do not perform plasma exchange in all patients with alveolar hemorrhage. As you know, this has been a really contentious issue. There's a lot of variation between centers, even before PEXIVAS, about what is actually done in terms of providing plasma exchange to all, some, or no patients who have alveolar hemorrhage.

And I think to really understand where we go next, we need to first define the goal of offering plasma exchange. The usual paradigm that I hear of is that patients with lung hemorrhage are at high risk of death. But I want to challenge that because there has been recent work that we've done with Dr. Lynn Fussner from the PEXIVAS data, as well as older work that we did with EUVAS data, that suggests that patients that have non-severe lung hemorrhage are really not at an increased risk of death compared to those without. So if you accept this, then there would be no reason to escalate therapy over the standard of care for patients with non-severe lung hemorrhage. The same issue is not, however, true for patients with severe lung hemorrhage. They have an increased risk of death. And again, Dr. Fussner's work helped support this, we hope to see it in publication soon.

So then the next question is, does plasma exchange reduce that risk of death? So from both PEXIVAS and from our metaanalysis, there's really no convincing evidence that plasma exchange reduces the risk of death in the subgroup of patients with alveolar

hemorrhage or in the overall patient population. However, we are fairly confident that plasma exchange increases the risk of serious infections. And infections are the most common cause of death in patients with severe lung hemorrhage, thanks to advances in supportive respiratory care. So I don't provide plasma exchange for alveolar hemorrhage in patients with ANCA-associated vasculitis when that's the sole indication. Rather, we provide it for patients who have alveolar hemorrhage, who are at also risk of kidney failure. In other words, I base the decision on providing plasmic exchange on the risk of kidney failure, and sometimes that includes patients with alveolar hemorrhage, and many times it does not.

Dr. Tesar:
Thank you. There is an important subgroup of patients with double positivity of ANCA and anti-GBM, and it is usually recommended that these patients should be treated in the same way as other patients with anti-GBM disease. So, is plasma exchange mandatory in all patients with double-positive ANCA and anti-GBM?

Dr. Walsh:
This is, of course, a really difficult question to try and answer. There's no RCT data to support or refute the utility of plasma exchange for these patients, and there likely never will be. And in fact, even the observational data is pretty small.

So, my approach is typically to try and base this decision on the most aggressive treatment guidelines, which are those are for anti-GBM disease, where plasma exchange is typically utilized unless the patient has both advanced sclerosis and fibrosis on the renal biopsy, and a very high creatinine that requires dialysis. And for many patients it's also based on whether or not they are oliguric. Some of those patients may have a more clear phenotype of being ANCA-associated vasculitis. Others may appear to be a more clear phenotype of anti-GBM disease, where they really just have a pulmonary renal syndrome or renal limited disease.

I think it's fair to use the anti-GBM guidelines and have an open discussion with patients about the likely risks and benefits in their particular case, even though this requires utilizing indirect evidence and extrapolating from two diseases.

So I'm sorry, it's not a very clear answer, but I would say that I tend to use plasma exchange for those who have this overlap syndrome of ANCA and anti-GBM disease, and we tend to use the same kind of criteria for not offering it for patients who look like they're very unlikely to respond to therapy and may have harm from it.

Dr. Tesar:
Thank you very much. There is now more and more commonly use of rituximab in patients with relapsing and also with newly diagnosed ANCA-associated vasculitis. So my last question concerns rituximab. How to use rituximab in patients treated also with plasma exchange?

Dr. Walsh:
Thanks, Vladimir. This is something that I think has really come to the forefront in the last few years as rituximab use has increased dramatically for the treatment of these patients. When we designed PEXIVAS, we didn't really have much data on this, and there weren't as many patients, not nearly as many patients, being treated with rituximab. We tried to make some kind of rudimentary guidance, in that we told patients - or we told providers not to perform plasma exchange within 48 hours of having infused rituximab.

There wasn't much to guide it. There's pharmacokinetic studies that show a very clear reduction in the half-life of rituximab when plasma exchange is done sooner than 48 hours after an infusion. But there isn't very much data at all on the pharmacodynamics and how they're affected by a plasma exchange, and essentially no data on clinical efficacy. From the PEXIVAS data, there was no interaction between the use of rituximab and plasma exchange, but that doesn't tell us that rituximab efficacy wasn't reduced by the use of plasma exchange, it just tells us that it wasn't any different whether or not we performed plasma exchange.

So I think that's pretty reasonable advice still. I do think we need to think fairly carefully about additional treatment with rituximab in patients who have refractory disease who received both rituximab and plasma exchange. But we kind of base those on each patient individually rather than coming up with any sort of uniform decisions about how we would use rituximab. So for right now, we still just wait the 48 hours after infusing rituximab before we could do another treatment to plasma exchange.

Dr. Tesar:
Many thanks. And before we close, Michael, are there any final messages or takeaways you'd like to leave with our listeners?

Dr. Walsh:
Yeah, I think the decision to use plasma exchange is still a bit confusing and not unlike before PEXIVAS or before other large trials in the area like MEPEX, we really need to base the decision based on the patient's risk of kidney failure, and our goal to reduce that risk using plasma exchange. So that means we need to be cognizant of what the actual risk of kidney failure is, and prognostic scores are becoming available to help us trying to find that risk.

At the same time, we do need to be aware and vigilant for serious infections, which is the most common cause of death for patients with ANCA-associated vasculitis. And by the fact that for many of us, there are costs and inconveniences to the treatment that can also affect the patient. But if we put all this information together, I think we can have actually a really good conversation with patients around whether or not the treatment should be useful for them. And we can make a really informed decision now.

Dr. Tesar:
That's a great way to round out our discussion today. I want to thank my guest, Dr. Michael Walsh, for joining me. Michael, it was really great having you on the program.

Dr. Walsh:
Thanks so much, Vladimir. I really enjoyed it, and all the best for the success of this podcast series.

Dr. Tesar:
Thank you. I'm Dr. Vladimir Tesar. To access this and other episodes in our series, visit KDIGO on Spotify or KDIGO.org/podcasts. Thank you for listening.