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Recent Progress in the Treatment of AAV and its Impact on the Outcome of the Patients

Announcer:
Welcome to this episode of KDIGO Conversations in Nephrology. This episode, titled Recent Progress in the Treatment of AAV and its Impact on the Outcome of the Patients 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 recent progress in treatment of ANCA-associated vasculitis is Dr. David Jayne. David is the Professor of Autoimmunity, and the Head of Vasculitis and Lupus Clinic in Addenbrooke's Hospital in Cambridge. David, welcome to the program.

Dr. Jayne:
Vladimir, thank you very much for this invitation, and I look forward to discussing this topic.

Dr. Tesar:
So David, my first question is, what is your definition of remission? When do you consider a patient to be in remission? We know that our patients with persistent signs and symptoms, so-called grumbling disease, and can these patients be also considered to be in remission?

Dr. Jayne:
So remission is important because if you fail to achieve remission, the outcomes for patients who are very much worse in terms of death or end-stage kidney disease. We consider three components in a remission definition: disease activity, the level of medications, especially steroids, and then time or period of observation.

Putting this into practice, when training physicians in vasculitis we can use the Birmingham Vasculitis Activity Score, which is an item list with definitions of features of vasculitic activity. And for remission to be defined, we really need an absence of any positive items using BVAS.

Concerning therapy, remission implies the patient has received a course of induction therapy, typically a course of rituximab or cyclophosphamide, and they're currently on a reducing steroid regimen, or may indeed have already stopped steroids. Although there – there's no precise steroid dose that we associate with remission, but it would be typically 10 milligrams a day or less of prednisone.

We then look to judge remission between 6 or 12 weeks, and then between 12 or 26 weeks. But in part, this reflects the insensitivity of the activity tools that we have in terms of defining absence of activity compared to presence.

Now you raise this question about grumbling disease, and this is particularly relevant to the kidney where we see persistence in urinary abnormalities, that is proteinuria or microscopic hematuria in around 50% of patients after 3 months of treatment. And there is a debate as to whether this means there is ongoing low level or grumbling nephritis or in fact, this is a result of previous inflammations or damage. We don't fully know the answer to that. But currently, if proteinuria and hematuria levels are stable or falling, and if the GFR is stable or rising, then that would be compatible with a remission definition.

Dr. Tesar:
Thank you for the explanation and we can now turn to the treatment. What are, in your opinion, the most significant changes in induction treatment of ANCA-associated vasculitis in the last decade or two? What emerging data on ANCA vasculitis are, in your opinion, most

compelling?

Dr. Jayne:
I think there are three particular areas of interest where there has been good data over the last decade. The first has really been a consolidation of evidence supporting rituximab in place of cyclophosphamide for induction, particularly for proteinase 3 ANCA. We've used rituximab, or have been studying rituximab for 20 years now. And it has been in the clinic for over a decade, but the data particularly for its use in maintenance is now much stronger.

The second topic is steroid dosing. Previously, we've recommended steroid dosing according to expert consensus, but we now have two quite high-quality trials comparing different steroid regimens. And we're now in a position to recommend a specific regimen and this, in fact, suggests we should be reducing steroids more quickly than we have done in the past.

And then the third area of interest, and this is the one that is the most compelling, has been the demonstration of the efficacy of complement inhibition in controlling vasculitis.

Dr. Tesar:
In your opinion, should rituximab be used in all patients with life or organ threatening ANCA-associated vasculitis? If not, which patients of this population should be chosen for treatment?

Dr. Jayne:
So this is an area of debate, and there are differences in opinion. But there is a lack of high-quality data using rituximab together with steroids for the most severe patients that's presenting with a low - very low GFR less than 10 to 15 or on dialysis or with severe lung hemorrhage. And because of that lack of data with rituximab, many physicians still or would prefer to use cyclophosphamide for those presentations.

We performed a trial which I think you took part in many years ago looking at the combination of rituximab with low-dose cyclophosphamide. And that regimen was clearly effective in terms of comparing it to longer-term cyclophosphamide, or is as effective as longer-term cyclophosphamide. And we now have a number of observational studies suggesting for these very severe patients, this combination seems to work.

The other element in all of this is steroid. And steroids are the major driver of adverse events. And these patients are at very high risk of adverse events, particularly infection. And the use of the combination, especially when compared to rituximab without cyclophosphamide, probably permits much more rapid steroid sparing. But this is an area, as I mentioned, of debate, and you'll find there are differences in opinion.

Dr. Tesar:
Many thanks. In your opinion, what is the potential of complement inhibition in ANCA-associated vasculitis?

Dr. Jayne:
So we clearly need newer drugs. Although we are able to achieve remission, that's at quite a price in terms of toxicity and it takes some time, as we discussed, in the initial points. Complement inhibition has been shown to be of importance to pathogenesis, where certainly in animal models, the alternative complement pathway is critical to the development of vasculitis. And we have quite extensive circumstantial data from the human disease that the alternative complement pathway is important. So we've got a good scientific background for using complement inhibition.

Dr. Tesar:
So we are now around the middle of our discussion, so for those who came later or who are just tuning in you are listening to KDIGO Conversations in Nephrology. Our topic today is the recent progress in the treatment of ANCA-associated vasculitis and its impact on the outcome of the patients. I'm Dr. Vladimir Tesar, and I'm speaking with Professor David Jayne.

So, we can proceed to the second part of our discussion, which is mostly concerned - of the maintenance treatment of ANCA-associated vasculitis. And my first question is, what are, once again in your opinion, the most significant changes to maintenance treatment in the last decade? And more specifically, what is the role of rituximab in maintenance treatment?

Dr. Jayne:
So, as a physician, you have to appreciate that ANCA vasculitis is usually a relapsing remitting disease, and you cannot simply stop treatment once patients achieve remission because the majority will relapse. We have learned over the last 20 years quite a bit about risk stratification. For example, patients with less severe renal disease have a higher relapse risk as to patients with PR3-ANCA. And conventionally, we've recommended oral immunosuppressives, with or without steroids, for up to 2 years.

We have also learned that when you stop immunosuppression for relapse prevention, the risk of relapse rises. And this has led to a debate about whether immunosuppressive treatment should be continued for longer than 2 years.

But what's changed now is that we have two randomized trials demonstrating rituximab is superior to azathioprine for the prevention of relapse; one predominantly in new patients using cyclophosphamide, and one in relapsing patients using rituximab induction. But the results of the trials are remarkably similar. And rituximab prevented relapse in around 90% of patients over the first 2 years. As a result of that in the upcoming 2022 EULAR recommendations for the treatment of ANCA vasculitis, rituximab is now the preferred maintenance regimen with a dose of 500 milligrams every 6 months. The uncertainties that persist is how long should you continue for. And there are two issues here. One is that once you start rituximab, within 6 to 12 months, the relapse risk returns. And the other is that for reasons we don't fully understand, ANCA vasculitis patients are at higher risk of a secondary immunodeficiency, i.e., low immunoglobulin levels following rituximab which can be irreversible.

With the COVID era, we've had the additional complications of the suppression of vaccine responses with rituximab.

So I think we're in this sort of situation where on the one hand, the data is strong, and we're recommending rituximab, but on the other hand, we are aware of some of the rituximab downsides. And this is leading physicians to spend more time thinking about whether they can personalize for an individual patient what they should do, and that in itself is not that easy. The biomarkers are not wholly reliable, that is ANCA or B cell counts.

Dr. Tesar:
You're saying that we should treat in a different way patients with anti-PR3 and anti-MPO vasculitis, I mean, in terms for instance of lengths of rituximab maintenance?

Dr. Jayne:
I think that's a great point. We know these diseases are genetically different although the phenotype can be remarkably similar. And we have previously noted a difference in relapse risk. But in the era of rituximab induction, there's really no good data of a big difference in relapse risk between MPO or PR3 vasculitis, especially if you control for the severity of renal disease. And you cannot rely on the fact that MPO-ANCA patients have a low relapse risk, they will relapse. And in the follow-up of the randomized trials that have been done on rituximab induction, there are many MPO-ANCA patients who relapsed. So I think for the purpose of this – of the recommendations, it's - there's no difference. At a practical level in the clinic, the MPO-ANCA patients tend to have more severe kidney disease. And that cuts both ways. On the one hand, they may have a slightly lower relapse risk. On the other hand, if they do relapse, the consequences could be very much worse in terms of end-stage kidney disease. So it's not an easy one to answer.

Dr. Tesar:
Thank you very much. And now I have my last question. So what is the future in the field of ANCA-associated vasculitis, especially in terms of treating more severe disease, such as advanced kidney disease or alveolar hemorrhage? And what are the major gaps we need to in some way overcome?

Dr. Jayne:
I think we have contributed to the data on treatment of severe kidney disease reasonably well. But where we lacked data is the treatment of alveolar hemorrhage. What we know, and this is particularly from the PEXIVAS trial, is that patients with alveolar hemorrhage who are not hypoxic, actually have very good outcomes. And that - their outcomes depend on their kidney disease. The patients with alveolar hemorrhage who are hypoxic, have a high risk of early death. And the debate there is does plasma exchange help? The numbers in PEXIVAS were too small to convincingly demonstrate a reduction in mortality but the hazard risk on the patients that were recruited, which is around about 60 patients with hypoxic lung hemorrhage was about 0.5. So there's a numeric signal, but it really needs to be confirmed.

And we also have concerns about the high comorbidity risks of these patients. They have a high thromboembolic risk and a high cardiovascular risk. That means myocardial infarction or stroke. And we have no good data at the moment to guide us and how we can reduce these comorbidity risks in these severely ill patients.

Dr. Tesar:
Thank you. And before we finish, David is there any final message or takeaway you'd like to leave with our listeners?

Dr. Jayne:
Yes, I think if you take a step back, much of the improvement in outcomes of ANCA vasculitis has been earlier referral to specialists, to nephrologists, or whoever. And I can't emphasize how important early referral is. The better the kidney function at the time of referral, the easier it is to control the patient and the better their long-term outcome, whatever treatment you use. So I think that's a really important point.

Dr. Tesar:
Thank you for this final message. I want to thank my guest, Dr. David Jayne, for joining me. David, it was great having you on the program.

Dr. Jayne:
Thank you very much, Vladimir.

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