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Should We Accept Status Quo for How We Have Treated PNH?

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Dr. Patel:
Welcome. Today we're going to talk about, should we accept status quo for how we treat PNH? Once again, I'm Dr. Bhumika Patel from Prisma Health, University of South Carolina in Greenville. And I'm here with Dr. Ilene Weitz.

Dr. Weitz:
Hi, I'm Dr. Ilene Weitz from the University of Southern California.

Dr. Patel:
So Dr. Weitz, we know with PNH being a rare disease and there's delays to diagnosis. However, now the treatment paradigm for PNH is expanding. How do you optimize, I guess, categorize patients, and with that we have C5s, we have eculizumab, ravulizumab, and now we have a C3 that was recently approved for PNH, pegcetacoplan. How do you sequence the complement inhibitors in treating your patients? Outside of insurance dilemmas that we have now, how do you prefer to treat your patients with newly diagnosed PNH?

Dr. Weitz:
Well, I think this is an area that remains a little uncertain at the present time. There is a large body of literature that's published on C5 inhibition, and a much smaller body of literature that's available on C3 inhibition with pegcetacoplan. We have recently started patients on pegcetacoplan who were naive. We're hoping that the data from the PRINCE study will be published soon. And which does suggest that you can treat patients up front with a C3 inhibitor with significant benefit, but that remains to be seen. There's no head-to-head trial. So it's completely a matter of one, how you want to approach the patient. And two, how the patient feels about treating themself. Because pegcetacoplan is dosed at home subcutaneously, twice or three times a week. On one hand, it gives the patient some flexibility, they can treat themselves. On the other hand, ravulizumab is given once every eight weeks and represents a huge convenience for the patient. And they don't have to come to the hospital, it can be done at home. So, why don't you tell us your experience with treatment with these agents?

Dr. Patel:
So from my experience with C5 inhibitors predominantly, because recently pegcetacoplan was... So normally, because there's long-term data with the C5 inhibitors, definitely with the approval of ravulizumab, we've been able to make it more convenient for our younger patients and even our patients that go to work to come in every eight weeks to get it. And I personally like them coming in every eight weeks, because you can monitor them closely. I have a handful of patients that were on C3 inhibition therapy with pegcetacoplan. And they were all compliant, and they did find the ease of administration at home. But I think the main concern I had with that was sometimes, if they did miss a dose, how do you compensate for that? And there were some patients that accidentally missed a dose. It wasn't intentional. And so, keeping a close eye on those patients that are at self-administration at home was one of the big key things in clinical practice that I kept maintaining to make sure they did not have any breakthrough hemolysis while on therapy, and they were

getting adequate control of their PNH on therapy. So I think it's exciting that we have three drugs now that we can use for patients, but to Dr. Weitz, as you mentioned, I do think that we need some upfront data from the PRINCE trial for us to know that, hey, pegcetacoplan is equally as efficacious as upfront C5 therapy for patients so that we can use it. As you know, we know that there's going to be patients who don't want to come in every eight weeks also to the clinic and want to be able to use therapies at home and follow up with their doctors and make sure their labs are doing well.

Dr. Weitz:
Although some patients can get their ravulizumab at home.

Dr. Patel:
That is true, yeah.

Dr. Weitz:
Or other patients because of their insurance status, they have to go to an infusion center. But there are some technical challenges sometimes with arranging home care, and that can be difficult. Whereas with pegcetacoplan, it's all set up. The biggest issue is, what if they have breakthrough on the pegcetacoplan and there is at least a plan to treat the patients with IV pegcetacoplan when they come to the hospital? But that's not an approved therapy. So I think, how to treat them for breakthrough is still somewhat unclear with the pegcetacoplan. And you don't want to have to mix drugs.

Dr. Patel:
Agreed, and I think that has been a challenge. And definitely with my past experience, we've had patients who are on C3 inhibition with breakthrough. How do you clinically manage those patients, right? And to your point, we don't want to mix C3 and C5 inhibition. Personally, I'm like, that's a lot of compliment inhibition from two different angles. And you worry about the risk of infections over time also, even though they're optimally vaccinated, but you don't want to have patients on two therapies. You definitely want to have them on one therapy to making sure that they're adequately controlled over time. And definitely, I agree with you. And I think with the IV formulation, that'll be something interesting to see the data for that, how that does help with the breakthrough hemolysis of patients on C3 inhibitions.

Dr. Weitz:
Right, I think there's just no data. And I know my hospital pharmacy and administration not going to let me just give IV pegcetacoplan without some data.

Dr. Patel:
Right, agreed.

Dr. Weitz:
So I think that's very... I think that's a big issue. But you could continue to treat with the patient's own therapy with C3, with pegcetacoplan. You just give it every day until they stop hemolyzing.

Dr. Patel:
Exactly, no, agreed. And so what are your thoughts in regards to, so now when you look at responses for patients with PNH on C5 therapy or C3, we have the risky counter criteria that we use for response to compliment inhibition. How is it incorporated in clinical practice for you? Because I don't feel like patients always meet one of those categories. They're somewhere in between those categories. What are your thoughts about that?

Dr. Weitz:
Well, most of the patients do get a response. And I think that the classification is somewhat limited in that most of the patients do have some form of response. There are very few that really don't respond. It's really that 20% of patients who remain transfusion dependent and it's pretty dramatic. They declare themselves very early. So, you know that patient, if they have ongoing need for transfusion, they will never respond to a C5 inhibitor. So you might as well switch them right then and there to a C3 inhibitor. Or down the road, factor B or factor D. I think that blocking the alternative pathway will be dramatic for those patients.

Dr. Patel:
Right. And a couple of things just to touch up on it and some of the topics we've talked about. For patients that have been initiated on C5 therapies, and we know about 20 to 30% of those patients may have ongoing symptomatic anemia or extravascular hemolysis with C3 deposition. How long do you wait while they're on C5 therapy before you switching them out to a C3 inhibitor such as pegcetacoplan?

Dr. Wietz:
Well, first of all, all patients on a C5 inhibitor will have evidence of extravascular clearance. It's just that they may not be anemic. They

have adequate marrow reserves. They're able to keep up. Their hemoglobins will be in a reasonable range and they don't experience the fatigue and all of those other complications or the thrombotic complications. That being said, if I have a patient who remains transfusion dependent, or their transfusion requirements increase even more, then I will think about switching them.
And how much time should you give? I don't think there are any rules to that, but pretty clear that the longest you should go would be three months. If you're using ravu, it's going to stick around for eight weeks. So then you'd give the patient eight weeks. If they have ongoing transfusion requirement, I think it probably not going to get better.

Dr. Patel:
In another topic that's not discussed much, especially with the approval of the complement inhibitors is the role of allogeneic stem cell transplant. How often do you refer your patients to bone marrow transplant for PNH? Because I think it's with classical PNH, and you have PNH arising for aplastic anemia. When do you consider referring to your patient's allogeneic stem cell transplant?

Dr. Weitz:
So most patients with PNH have some component of less than adequate bone marrow response, which is why they may stay anemic, not everybody. But in those in whom aplasia, if they present with a small PNH clone and their aplastic, we would probably get them started. And then with treatment for their aplastic anemia and see if their PNH clone expands. In those in whom it expands, then they would go on treatment. But I do refer patients with PNH for transplant, particularly if they're really young, and they have a prominent aplastic component. I think, for patients who have pure hemolytic PNH, classical PNH, I really don't refer them unless they fail to respond to treatment.

Dr. Patel:
Yes. And I agree with you on that. Usually all my younger patients and up to even older patients with aplastic PNH, any component of that, combination of that, I refer everyone to transplant, at least get evaluation, and depending on their response and assess, if they need to go to transplant or not.

Dr. Weitz:
Yeah, we have done I think two patients who were over 50 got transplanted because they had good matches. Sibling matches. But that is relatively rare. But anybody who's young, they're going to have a lifetime of this disease. Why do you want to go there?With potential for complications. So, I would recommend those patients be evaluated for transplant.

Dr. Patel:
Well, thank you so much, Dr. Weitz, for this dynamic discussion. It's always great to talk to other experts in the field. And really appreciate you being here. And this will be end of our episode. Thank you very much.

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