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

Examining the Treatment Paradigm for Paroxysmal Nocturnal Hemoglobinuria

Announcer:
You're listening to *Project Oncology* on ReachMD. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD. I'm Dr. Charles Turck. And joining me to discuss the treatment landscape for paroxysmal nocturnal hemoglobinuria, or PNH for short, is Dr. Brian Mulherin, who is a hematology and oncology specialist at Hematology Oncology of Indiana and Ascension St. Vincent Hospital in Indianapolis. Dr. Mulherin, thanks for being here today.

Dr. Mulherin:
Thanks for having me.

Dr. Turck:
To start us off, Dr. Mulherin, what can you tell us about the current treatment landscape for PNH?

Dr. Mulherin:
So we're going to confine our comments to patients with classic hemolytic PNH, meaning PNH not associated with another bone marrow failure syndrome, although there is an element of marrow failure in all these patients we think or in patients with subclinical PNH clones. Assuming we're looking at that, there are three approved treatment options. Keep in mind that these do not change the underlying genetic defect. These patients have PNH because they have this acquired somatic mutation of the X-linked PIG-A gene. This does not change any of that. We're just trying to prevent complement-induced lysis. So there are three options. We have eculizumab, which is I.V. administered every two weeks; we have ravulizumab, which is I.V. administered every eight weeks; and then we have pegcetacoplan, which is a subcutaneous infusion that patients can do at home.

Eculizumab and ravulizumab act more distally or lower in the complements cascade; they inhibit C5. Pegcetacoplan acts more proximally by inhibiting C3. There are distinctions here. If C5 only is inhibited, C3, through the process of takeover, can still deposit on red cells, and C3 is a potent oxidant. So these red cells can be phagocytosed by components of the reticuloendothelial system, so the liver, the spleen, and that's called extravascular hemolysis. C5 inhibition by eculizumab and ravulizumab pretty effectively controls intravascular hemolysis.

Patients are going to be differentially sensitive to these. Some patients who are on a C5 inhibitor don't have any significant residual hemolysis, or very little residual hemolysis at all, and some have quite a lot. Probably 30 to 40 percent of patients on C5 inhibition are going to have some degree of anemia, and some may even be transfusion dependent.

How do you pick that though? How do you know from the beginning which is going to be the more effective? Or the most acceptable route for the patient? Keeping in mind the different modes of administration; maybe I.V. every eight weeks with ravulizumab being more common versus having patients do subcutaneous infusions twice a week at home. As of right now, we do not have a good answer to that question.

Dr. Turck:
So then, let's take a closer look at these therapies. How do they compare with one another when it comes to their efficacy?

Dr. Mulherin:
So in terms of control of hemolysis, anything which is going to act upstream to the compliments gap cascade or more proximally is

going to be more effective at suppressing hemolysis. If you're looking at the difference between a C3 and C5 inhibitor, one of the questions is does that matter for all patients? So some patients do extremely well with eculizumab and ravulizumab. So again, just to recap, the average age at diagnosis for this disease is around 39. These patients are young adults, early, middle aged. So they are typically in the workforce, they may have young children. So if they get very fatigued, they cannot function, they cannot perform their instrumental activities of daily living, it's going to have an outsize impact on them and on their communities on the individuals that they interact with.

So some patients do extremely well with eculizumab and ravulizumab, but some do not. Probably around 30 to 40 percent of patients still have some significant anemia, despite treatment with C5 inhibitors. That's because we still have C3 being active and depositing on red cell surfaces and serving as a potent oxidant. So those red cells can be destroyed in the reticuloendothelial system, that's extravascular hemolysis.

So we do have another drug, which can be used in that setting, pegcetacoplan. It requires administration, which can typically be done at home, twice a week, through as of right now anyway, through an infusion pump.

So what is the best way of picking how one is going to respond to one versus the other? We don't have a great way of making the determination diagnosis who's going to respond well to one versus the other. There could be compliance issues there. So if you're worried that someone is not going to take pegcetacoplan twice a week on a regular basis, then they should probably not receive that drug. They may be better off receiving directly observed therapy - eculizumab or ravulizumab.

If there are patient access concerns, copay assistance, those kinds of things, then something which is part of their major medical coverage, like eculizumab or ravulizumab, may be the better option. Although many of these patients are younger, and so they are less likely to be on Medicare. So most of these are going to be eligible for manufacturers subsidized copay assistance and things of that nature.

I guess it's very difficult to know which one right now. We've got these three options. Which one is the best one to use when someone is first diagnosed? Now if someone is on a C5 inhibitor and does not respond well, still has significant residual symptoms, we have level one evidence to show that pegcetacoplan is the better drug in those cases from the PEGASUS trial, which showed significantly improvement in anemia and improvement in quality of life, etcetera, in those settings. What's more difficult to determine is how do you pick at diagnosis? Who's going to respond better or going to respond to which drug the best?

Dr. Turck:
And how about their safety, what toxicities or side effects should we watch out for?

Dr. Mulherin:
So all three approved complement inhibitors, pegcetacoplan, ravulizumab, and eculizumab, are broadly similar; one would be obvious, their administration reaction. So eculizumab and ravulizumab, there's a rare chance for having infusion reaction. That is not very, very common though; it can happen. You're not going to have the same type of reaction with pegcetacoplan since it's administered subcutaneously twice a week through a home and through an infusion pump. But people can have injection site reactions to that. In PEGASUS and PRINCE for example, probably around 30 to 40 percent of patients had infusion reactions to pegcetacoplan, but they were typically mild to moderate, and actually typically tend to go away or to significantly improve after the first few periods of use as patients become more comfortable using it.

Aside from that, many of the reactions are quite similar. There's a risk for infection that is comparable to both. There's black box warnings, for a risk for infection of encapsulated bacteria. So before patients start, they must be vaccinated against Strep pneumo, Haemophilus influenza, and then the two broad different serogroups of Neisseria meningitidis. But that is common to all of these drugs, and there are specific ACIP protocols that are available for vaccination requirements for these patients.

One maybe theoretical concern was well, if you're inhibiting the complement cascade more proximately, like C3 for example, are you going to be at risk for some additional immunodeficiencies and longer-term effects? Again, the only drug that is approved right now in that setting is pegcetacoplan, but there are many others on the way. As of right now, we have not seen any evidence of that the infection risk seems to be comparable between them. There aren't any cases of infections with encapsulated bacteria that had been reported so far in the PEGASUS or PRINCE trials for example. So as of right now, really these in terms of side effects, these seem to have far more similarities than differences minus their different routes of administration, I.V. versus sub-q at home.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck. And I'm speaking with Dr. Brian Mulherin about the current PNH treatment landscape.

What more could you tell us about patient access considerations that we should keep in mind when it comes to prescribing these therapies?

Dr. Mulherin:
So a few things. Number one, these therapies have to be taken indefinitely. Again, assuming we're thinking only of classic hemolytic PNH, and they're not going to be able to stop. The PNH clone is still going to be there, and they will still hemolyze if the therapy is stopped. For whatever reason, the therapy might be stopped because the patient doesn't take it because of insurance, access issues, etcetera. So that's number one.

Number two, these therapies are very expensive. They all cost more than $450,000 a year. So access can sometimes be a challenge. That being said, most of these patients are younger. So they are typically in the upper 30s or 40s when they're diagnosed. And so they are eligible for most of the assistance programs that the manufacturers have available. Eculizumab and ravulizumab are administered in the office, they're part of their major medical coverage. If patients were of Medicare age, we would call that Medicare Part B. Pegcetacoplan is administered at home as part or can be administered at home, typically is administered at home by the patient, as part of their prescription drug benefit. If they had Medicare, again, we would call that Part D. So there could be cases where one person's insurance plan may prefer one versus the other. That being said, the manufacturers have multiple assistance mechanisms to ensure that patients are able to get the therapy that they need. I cannot recall a time where I was not able to get a patient on some type of therapy. If they have PNH and they need a complement inhibitor, keep trying. One way or another the patient will be able to get on therapy. It might just take a little bit of doing.

Dr. Turck:
And as we end our discussion today, Dr. Mulherin, do you have any closing thoughts you'd like to share with our audience?

Dr. Mulherin:
This is again, an ultra-rare disease, and we cannot change the underlying mechanism. These patients have a somatic mutation in PIG-A. And so these are complement inhibitors, we aren't changing the underlying problem. That being said, we can give patients hopefully a normal life expectancy with a very good quality of life so long as they get the appropriate therapy and the appropriate therapy that works best for them and for their own circumstances. That's number one. And then number two, stay tuned. There's lots and lots and lots of new drugs, which are in development for this disease. Right now, the main question is between C5 and C3 inhibitors, but it's going to get much more complicated in the future as we have other drugs which are becoming available, including some oral drugs. And that brings up a whole host of new questions that we as a community will have to answer.

Dr. Turck:
Well as those final thoughts bring us to the end of today's program, I want to thank my guest, Dr. Brian Mulherin, for joining me to discuss the current treatment options available for PNH. Dr. Mulherin, it was great speaking with you today.

Dr. Mulherin:
Thank you very much for having me.

Announcer:
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