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

If We Are Rethinking the Risk Tiers in PAH, Do We Also Need To Rethink Management Strategy?

Dr. McLaughlin:
So, if we are rethinking the risk tiers in PAH, do we also need to rethink the management strategy? I'd really like to emphasize, we're doing better with our risk assessment, now we're refining that intermediate-risk group. It's not just green, yellow, and red anymore, we need to think about the shades from light yellow, through orange to deep orange in that intermediate-risk group. Because I do think that group is very, very heterogeneous and it does influence our treatment decision. Those patients at the higher end of intermediate-risk may act more like high-risk patients, they may have a poor prognosis, they may benefit from more aggressive therapy. So as we think about our intermediate risk patients, we have a variety of treatment options for them. Those patients more to the left of intermediate may be appropriate for dual oral therapy, but those patients who are more orange might be more appropriate for combination therapy, triple combination therapy that includes a parental prostacyclin up front. So we really need to try to explain this to our patients and really have a conversation of risks and benefits and shared decision making. We know that there are risks and uncertainties about the potential benefits for maximal medical therapy, including parental prostacyclin in some of those more intermediate risk patients. But I would argue that that recent French data helps us. I think it was pretty impressive looking at the benefit of upfront triple therapy with the parental prostacyclin in that intermediate risk group. So to me, I feel like that's a really wide group and I think about them very differently now and I think the four strata approach helps them. I think no matter what you decide to do with that baseline time. And I know I've been there. So many of my patients who I'll call orange patients or intermediate high-risk patients, despite me talking very passionately about the improvement in prognosis with combination therapy that includes a parenteral prostanoid that they look at me and they say, hey, anything, but the pump, let me try something, but the pump. And I think that's okay as long as you watch them closely. And we are very aggressive now about reassessing those patients within three months and then talking again about the parenteral prostanoid if they're still in the intermediate risk, or especially if they're on the more orange side of intermediate risk.

Initiation of triple sequential oral combination therapy may be appropriate for some patients who are not in the high risk. And I think it's really important to remember that that even though I'm touting our risk assessment, we've learned a lot about it. It's not perfect, and the person who keeps me up at night is that younger person, you know, that 18 or 20-year-old who otherwise is in really good shape and they walk over 440 meters, it may be that they're predicted as 700 and they walk 450. So they score well on the risk assessment tools, but they're still not where they should be. So they may have pretty good symptoms because they're otherwise in good shape, but they're sick, they have a high PVR, they have RV dysfunction. Those patients worry me. So sometimes we get a little bit more aggressive in those patients and go to triple therapy may not be parental process cycline, but maybe an oral prostacyclin, even though they're still functional class two. While there are other patients who may have other phenotypical characteristics that convey a poor prognosis and things like a connective tissue disease who may benefit from sequential combination therapy. And of course, the IV prostanoid should be included in combination therapy for high, and some of the intermediate-risk patients at the time of diagnosis.

Again, let's highlight the French pulmonary hypertension registry. Again, this is such an easy methodology just for characteristics and just counting those four characteristics, functional class, walk greater than 440, right atrial pressure, less than eight, and cardiac index of greater than 2.5. And the impact of initial therapy on survival was analyzed in a subset of those patients treated with initial therapy with parental prostacyclin. And as you can see, there were a chunk of patients, 76 treated with triple combination therapy, 5% of the population, the majority were treated with monotherapy and about a third of the patients with dual therapy.

And here is how their risk assessment changes, again using the four-risk model, the four different criteria. And on the left, we see where they were at baseline and the right, we see where they are at the time of first follow up. And the goal here is looking at patients who get to low risk status. So you can see here's the risk assessments on the left. And at the time of first follow up, you can see a higher proportion of patients on triple combination therapy got into the green zone, about 40% of them had four low risk criteria where on dual therapy, it was less than 20% and on monotherapy, it was only about 13%. So I think the point of this is that they're even the sickest of the sick are the ones that get initiated on triple combination therapy. It's very efficacious and you see the highest proportion of patients that get with four low-risk criteria. And you can see that over 70% of these patients actually get to three or four low-risk criteria, which is what they consider to be low risk. So it really emphasizes the potency of combination therapy that includes a parental prostacyclin.

And here is the overall survival in that population, on the left, you see all patients together. And I think it's really heartening to me to look at this, we think we've come so far with our pH therapies, and we have, we're doing so much better than we used to do, but we still have a long ways to go. You can see the one, three, five and 10-year survival in the overall study population was 93, 77, 62% at five years, 44% of 10 years we still have a long way to go. And on the right, you can see the survival of those patients that were treated based on the initial treatment choice. So in red, you see the triple combination group and you can see despite the fact that those patients were probably sicker, mind you they were also younger so I want to put a little bit of fair balance on that. The patients who were treated with triple combination therapy had much better survival than the patients who were treated with dual or monotherapy. So I think it's really important to consider this, particularly in the sicker patients, the high risk or the intermediate-high risk.

In the French registry, initial triple combination therapy that included a French prostacyclin was associated with better long-term survival. For the most severe patients, this was limited to patients with idiopathic heritable, anorexigen-induced PAH, transplant free survival was higher in this group. And this study really supports the utility of multidimensional risk stratification to help choose the most appropriate patients for these various treatments. For the intermediate risk patients at diagnosis, dual combination therapy was better than mono combination or monotherapy, but as I showed earlier, this was the first study to show a difference in outcomes in the intermediate risk group treated with parental prostacyclin therapy. So I really think this is quite important. I think it's also nice to see that in a high-risk patient population, you saw the difference, you know, the treatment algorithm and the 6th World Symposium is really based on experience, and then this puts a little bit of data behind that. Now, I also want to mention the Triton study because that was a study of upfront triple oral therapy that included versus placebo. There was not a difference in the primary endpoint in that the primary endpoint was PVR. And one of the exploratory endpoints, there was a signal for a difference in outcome. So, I think that's something we need to keep in mind.

Why not just get everyone upfront triple therapy? Well, I think there's pros and cons of this. You know, there's certainly a lot of evidence to suggest that the timing of therapy matters. Certainly, we've seen clinical trials that showed that the patients randomized placebo never caught up. And so, it may not be a wise idea to delay therapy. And that's why, even if we don't start with triple therapy or aggressive therapy upfront, I'm really pushing for that reevaluation to be sooner at three months, rather than six months. We know that clinical worsening, waiting till a clinical worsening event is not good, we know clinical worsening is associated with increased mortality, so we don't want to wait until something bad happens. We know that mortality is higher in the incident versus the prevalent patients. I think we have the greatest opportunity to make an impact earlier in the disease. We know that the majority of PAH patients newly diagnosed fall into the intermediate-risk category, and so treating them more aggressively, especially those on the higher end of intermediate-risk may be important. So, there's a lot of reasons to do that, but I think there are reasons why we need to be more cautious. We need to acknowledge the limitations in the French registry, or perhaps the people who were treated with more aggressive therapy were younger, there were more women, and maybe there were some other variables that impacted their good prognosis or contributed to that. We know that triple combination therapy may have cost, maybe we shouldn't apply this to all groups of PAH patients. And of course, cautionary measures about the results of Triton.