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Time needed to complete: 43m

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Macitentan Update: Impact on Management of Pulmonary Hypertension

Announcer:
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Dr. Channick:
Welcome to this Journal Club. Today, I'm reviewing the latest evidence from the macitentan trials and the advantage of fixed-dose therapy in clinical practice.

This is CME on ReachMD, and I'm Dr. Rich Channick.

As you may know, if you've been doing this for a while, the value of combination therapy in pulmonary artery hypertension is really unquestioned at this point. Treatment algorithms based on very large long-term studies of combination therapies of pulmonary arterial hypertension have very consistently shown benefit to using these drug combinations. And as you know, we now actually have drugs that work through 4 different pathways in the pulmonary vasculature. So we certainly have the option to combine these therapies. And very consistently, it seems like there's a benefit for the currently approved therapies.

So we need to understand how we use these therapies, when we use which combination. And I do think that the treatment guidelines kind of give a lot of evidence for that. One of the evolutions that we've had is going from what we call sequential combination therapy, so starting drug A and then adding drug B and drug C, and now maybe drug D, is one approach. And there is some data that shows that that can be of benefit.

As it relates to macitentan, the original SERAPHIN study, 2/3 of those patients were on background therapy, and then macitentan was an add-on therapy. So in that case, add-on therapy with macitentan did improve their primary endpoint; it was a composite endpoint, morbidity/mortality endpoint. So certainly, there is a role for sort of add-on therapy, sequential add-on therapy.

But then there were studies subsequently that showed there may even be more of a benefit to combination therapy up front. So in other words, starting drug A and B initially, and in many cases, as the guidelines suggest, that would be an endothelin receptor antagonist and a drug working through nitric oxide, so a PDE5 inhibitor. And those data suggested that by doing that, starting those 2 drugs up front, those 2 classes of drugs, you could get a significant benefit, not just preventing worsening of the disease, but actually having more patients improve.

So that really heralded, I think, the era of so-called up-front combination therapy, to the point where most patients are now started on 2-drug combinations, and then we increase from there. There are, in fact, some patients where, the sicker patients, where even a 3-drug up-front combination therapy is important.

Now, you know, drugs have side effects and they're also, you know, the more pills you use, the harder it is. I mean, if you're on medication, you'll know that it's – even to remember to take the medications together or forgetting, it's obviously a huge problem in medicine.

So I think that the concept of a fixed-dose combination of giving 1 pill that has 2 of the medications, I think, has real appeal. You know, obviously, it's based on the premise that those 2 drugs should be used together and are effective together. And that's where all the background related to combinations, up-front combinations of ERA, PDE5 inhibitor really give the background or the ammunition to wanting to develop a fixed-dose combination regimen.

So with that in mind, the combination of macitentan and tadalafil became

of interest to develop that combination. Now these are both long-acting drugs, so they're both once-a-day therapies, typically. So therefore, it's feasible to design a pill that has both of those agents in it that you would just take once a day. And so that was the idea. So the macitentan/tadalafil combination pill was developed and then was tested both for safety and for efficacy.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Rich Channick, and I'm reviewing the latest evidence for the macitentan trials and the advantages of fixed-dose therapy in clinical practice.

The A DUE study, A D-U-E, was a study evaluating fixed-dose combination therapy. And when we think about it, it's getting into the weeds a little bit, but macitentan is only approved at 1 dose, 10 mg. Tadalafil can be given as a 20-mg tablet once or twice, 1 or 2 pills a day, so either 20 or 40 mg per day, depending on side effects. And we'll talk about side effects in a second. But that was the algorithm for the study, the protocol where patients would get the combination of 10 mg of macitentan and 20 mg of tadalafil as sort of a run-in. If they tolerated that, then they would go to the 10-mg/40-mg combination pill, which would be kind of the maintenance pill.

And so that was the study. Now the results of the study actually were pretty reassuring. A, the combination was tolerated. Now what about side effects? So we know macitentan has side effects, including peripheral edema, nasal symptoms, reflux, in some cases headache. Tadalafil, a PDE5, has got very similar side effects with peripheral edema in some cases, but things like reflux, headache, etc. So there is obviously the possibility that the combination, you know, can give you more side effects, and certainly that can be the case. But in general, what emerged was very compatible with what's been seen with these drugs in the past. There were no real surprises related to side effects. And the vast majority of patients tolerated the combination really quite well without any, you know without major issues. So it did appear very feasible that a fixed-dose combination could be taken together.

The other nice thing about this A DUE study, is that there actually was a nice hemodynamic effect of the combination. So one could actually see that the combination of macitentan and tadalafil gave a significant hemodynamic effect with improvement in pulmonary vascular resistance, as a combination. It was an additive effect. So I think it's sort of similar to what we thought with other combinations. But this was a really nice demonstration with invasive hemodynamics, showing that 2 drugs actually do work better in improving pulmonary vascular resistance in hemodynamics, which, of course, is ultimately what our goal is, because we're treating pulmonary hypertension.

And the patients feel better as well, which is great, but as a physician, it's really reassuring to actually see objective improvements in things like cardiopulmonary hemodynamics, and so that combination definitely did that. And so I think that, with that in mind, it got approved as a fixed-dose combination that's now available. Again, I don't think there's any question about the benefits of combination therapy.

How do we use it in our practices? Well, it's actually not too hard, because certainly for patients who are maintained on or already on macitentan and tadalafil, or an ERA and a PDE5 inhibitor, it's simple to just switch them over to this fixed-dose combination. And it has not been particularly problematic.

For patients just starting therapy, we do have a couple options, and there's certainly many patients that we're going right to the fixed-dose combination, somebody that I'm confident is going to tolerate the therapies. Some of the patients we have to be more careful with, like older patients, you may have some comorbidities where it may be, in fact, better to start one of the drugs and then add the second one, depending on side effects and tolerance. And then once you get into that stable combination, then you go to the fixed-dose combination. I think that's perfectly appropriate for some of these more fragile patients and the older patients.

But for the majority of patients, I would say we just start with it, and we do the 10/20 combination for a week or so. And if they tolerate that, we go to the 10/40 combination. So it seems like it's been working quite well. As I said, the side effects we're seeing are similar to what we see with the drugs individually, not surprisingly.

So, well, I think that there's real potential for this fixed-dose combination. I mean, we even had patients who are on a shorter-acting PDE5 inhibitor, like sildenafil, where we'll then switch them to the combination with the once-a-day tadalafil preparation, and they seem to have done well, anecdotally.

So I think it is a really welcome advance in the field, which is moving forward rapidly. Again, these are 2 drugs that are already available,

but now that we can use them together, it simplifies things, and certainly the patients are very happy to have some easing of the pill burden.

That's all the time we have for today. Thanks for listening.

Announcer:
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