THE Cardiology Advisor

How I Treat With Sacubitril/Valsartan for Heart Failure With Reduced Ejection Fraction

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Dr Rouf: So just to introduce ourselves, I'm an advanced heart failure (HF) physician and Zane is an internal medicine physician. We are going to present the case of a 70-year-old female patient who I've been treating for HF since September of 2017. She initially came to me after having been discharged from the hospital for HF. She had been having symptoms of shortness of breath and when she presented to my clinic, she was already on good medications for HF, including metroprolol XL and lisinopril. Over the course of her outpatient care we were able to continue to optimize the doses of her medicines. She was successfully staying out of the hospital without symptoms of HF and doing very well.

In approximately March of 2019 we were discussing whether it was an opportunity and a good time for her to be switched from lisinopril to a newer medication, sacubitril/valsartan, and our discussions about that medication began at that point. During that time, we actually encountered a number of challenges that I thought would be very helpful to share with internists and primary care physicians who are thinking about putting their patients on these medications in particular.

We started our patient on the path of switching from lisinopril to sacubitril/valsartan. She was one of the first patients whom I was putting on this medication, and when she was starting the medicine, we had the opportunity to give her a 30-day free trial. However, when she returned to the pharmacy her co-pay for the medication was nearly $400 each month. She was unable to afford the medication and we actually ended up having to switch her sacubitril/valsartan back to lisinopril while we were sorting through the financial options for her.

This story has a happy ending. We were able to get her some financial assistance. Also, further investigation revealed that her monthly co-pay ultimately would not be $400 but instead something closer to $40. It was still more expensive than some of her medicines, but at least it was affordable for her. She is actually doing very well right now. She is on a good medical regimen including the sacubitril/valsartan, and she represents the type of patient we can put on this particular medication.

Dr Gowani: Rosanne, when I think about my patient population in the clinic, I have quite a few patients who are around the same age as your patient who have reasonably stable HF. How did you pick this particular patient?

Dr Rouf: As you know, HF is a very complex diagnosis. A lot of patients are diagnosed with HF. However, not everybody who has HF should be placed on this particular medication. What made this patient a candidate for sacubitril/valsartan was that she actually presented to the hospital with active signs of congestive heart failure (CHF).

As you know, there are several stages of HF. Our patient was at Stage C HF, which is defined by the American Heart Association (AHA) as having structural heart disease with symptoms of CHF and signs of volume overload. Sacubitril/valsartan is not a medication that you start for patients with HF who have never had signs of congestion. It's a medication that you start for patients who have had symptoms of CHF, either in their past or currently.

The first study that revealed the benefit of this particular drug in patients with HF was PARADIGM-HF, which was published in 2014 in the *New England Journal of Medicine*. Their protocol was for starting these medicines in an outpatient population of individuals with New York Heart Association (NYHA) class II symptoms. What that essentially means is that these patients are fairly active but still have some signs of shortness of breath with a lot more exertion. For example, this particular patient was able to climb 2 flights of stairs without getting short of breath, but if she did much more than that she would get short of breath compared with colleagues or friends of hers. So she was aware that she was not able to keep up with friends, but she was able to at least do that. Therefore, according to our definition of classes of symptoms, she would be considered NYHA class II.

Dr Gowani: This is the kind of patient who may walk their more sedentary dog, for example, but doesn't go out and do all their grocery shopping themselves. Does that sound about right?

Dr Rouf: So a patient like that might be closer to NYHA class III. So these are typically still fairly active patients. They do have symptoms, but they have noticed a change in what they can do similar to what you are describing. Someone who can't do their own grocery shopping is closer actually to NYHA class III as they are much more symptomatic. However, they are still able to talk to you and have a discussion. Patients with NYHA class III HF more likely cannot walk 2 flights of stairs at the same pace as their spouse, for example, who might be healthy, and they can't walk their dog without getting very, very tired. But a patient with NYHA class II HF almost sounds like an asymptomatic patient with NYHA class I HR, but not quite.

Dr Gowani: So when I think about the patients who see me after a hospitalization for HR, I find some challenges with the HF in and of itself. As you mentioned, the AHA stages are sometimes a little bit confusing for internists to call something HF before congestive symptoms are present. One of the struggles I have is that patients will come to my clinic

being treated for CHF and sometimes not even being told that they indeed have HF. I find that when you're talking about adding new medicines, particularly a brand-new medicine like sacubitril/valsartan, it's difficult to broach that subject when you also have to broach the subject of introducing the concept of HF.

Dr Rouf: Oh, that's definitely a challenge. Even as an advanced HF physician, usually I'm the last stop on the train of all the physicians that some of these patients do see. It is definitely a challenge even when they come to my clinic. So I certainly understand that. And I don't think it's a challenge that will go away. I think it is the responsibility of all of us who care for the patient to be proactive in telling patients who have had an episode of CHF that they have CHF or HF.

It's a very difficult term to relay as physicians to your patient because it sounds bad. It is a difficult diagnosis, but without empowering the patient with that knowledge, you're correct in that we can't have the other positive discussions about how we as clinicians can help these patients be able to live with this chronic illness. Some of the terms that patients may sometimes hear instead of HF are fluid overload, volume overload, or "your heart can't keep up with your body's needs." These are all code words for HF.

Dr Gowani: Another challenge I have with patients who come to my clinic with CHF is they are on a lot of medications, particularly if they have CHF with reduced ejection fraction. They may be taking 3 or 4 medications, and when you're thinking about the generally older population that this is, I worry about their ability to name and take care of their medications. I worry about the medications interacting with other medications they may take such as those for chronic pain or those for other symptoms that come with old age. And then finally, as you've already mentioned, I worry about costs for our patients. How do you distinguish those 3 things?

Dr Rouf: I think the easiest issue especially with this particular drug is the cost issue. There aren't too many interactions with other medicines that I have come across in the care of my patients and I now have approximately 25% of my patients with HF taking sacubitril/valsartan.

But cost is probably the biggest issue to address when introducing this medicine to patients with HF with reduced ejection fraction. I had a couple of cases where patients were introduced to the medication and then found out later that they could not afford it. So, I now actually introduce the medicine as an option. There are 3 medications that all have class I recommendations according to the AHA/ACC; the other 2 medicines are medicines that many of my patients with HF with reduced ejection fraction are on (either an angiotensin-converting enzyme inhibitor [ACE] inhibitor or an angiotensin receptor blocker [ARB]). My center program that I mentioned earlier uses an ACE inhibitor.

When I introduce the medicine, I introduce the possibility that it could be cost-prohibitive for the patient, but that we are going to work with them to look into what the options are. If we are able to put them on the medicine and they are able to afford it, we

do say that that's our preference. But we also reassure the patient that if they cannot afford the medicine, then the ACE inhibitor or ARB are also viable, very good options as well.

Again, these are the challenges whenever a new medication has been introduced, and it has proprietary use and has all of these challenges with cost, but we work with our patients. If you are an internist or a primary care physician in a practice, it would help to onboard your team and staff as to the benefits of the medication and prioritize a plan for seeking financial assistance or working with patient programs to help patients afford the medicines. That is also something that I think is very appealing to practices in our community in terms of trying to get patients on the best possible medical regimen to reduce hospitalization for HF, which is costly, as well as to improve their quality of life and their mortality. So appealing to those causes helps your hospital and helps your practice get on board with finding ways to help patients afford those medicines.

Dr Gowani: So practically speaking, if I'm going about my patient panel thinking about the patients that I want to try to switch to sacubitril/valsartan, I'm thinking about patients who generally know their medications, have at least an ability to afford it with their insurance, and have not had substantial interactions with their cardiac medications or with other medications. Once I go about picking that patient, what do we do next? How do you actually start the initiation process?

Dr Rouf: I first make sure that they don't have any contraindications to the medicine; an important one is if the patient has had a history of angioedema to an ACE inhibitor, which is a very strong black box indication. And there are several other contraindications. We set our team in motion to figure out if the patient can afford the medicine. Once they've cleared that hurdle, then we have a very important discussion with the patient, particularly if they are on an ACE inhibitor. It is important for patients to be off treatment with an ACE inhibitor for at least 36 hours before they start sacubitril/valsartan. In the earlier trials, when they actually combined the class of medications that sacubitril/valsartan is in with ACE inhibitors, there was an increased risk for increased prevalence of angioedema. So it is very important for them to have cleared the ACE inhibitor out of their system before they start sacubitril/valsartan.

I actually prefer that say 48 hours, because it's easier for me to relay that to other primary care physicians and internists, as well as the patient. It is easy to understand that you need to stop lisinopril or an ACE inhibitor on Monday, don’t take it on Tuesday, and start sacubitril/valsartan on Wednesday. The other thing to remind them is that while they were probably on a once-a-day drug like an ACE inhibitor or an ARB, when they switch over to sacubitril/valsartan it's actually a twice-a-day drug.

We have this conversation 2times: we do it in person when I initially introduce the possibility of switching them to the medicine and when I discuss what it's going to entail for them. And then we do it again once we are certain that the patient is able to afford the

medicine: when we've ordered the medication, and the authorizations that are initiated by our staff are cleared through the pharmacy. Our nursing staff will then call the patient and remind them that they should not overlap the medications. We also tell the patient, "Hide your bottle of ACE inhibitor in your underwear drawer or throw it away." Often, as you know, elderly patients will fill their pill boxes and forget. They will take all of their medications. So we just remind them to go hide the ACE inhibitors that there is no accidental ingestion of both medications at the same time.

Dr Gowani: Generally, when I have patients who utilize pill boxes and I'm starting a new medication, I'll have them come in and I will fill the pill box for them with the new medication. Let's say one of my patients sees a cardiologist or actually is in the hospital for CHF and gets started on sacubitril/valsartan, which we now seen after the PIONEER trial. I then see this patient on hospital discharge with their next primary care appointment. How do I go about evaluating that they're tolerating the medicine, and whether or not I should titrate that medicine?

Dr Rouf: That's a very great point. So, the results of PIONEER-HF were published in the past few months. The main issue is that if you see a patient who has been discharged on this medicine, you must ask the patient if they're taking the medication. It is uncertain whether patients continue taking these medications. As I said earlier, cost is sometimes appropriate or it may be a prohibitive issue with the medication. We have had patients come back to our clinic discharged on sacubitril/valsartan, which is a new medication for them, and it turns out they actually never filled the prescription because they realized when they got to the pharmacy that they could not afford it.

So, step 1 is to make sure they're taking it. Step 2 is that if they're not, verify that it wasn't an appropriate medication that would be actually good for them. If they're stable, coming to your clinic, not actively in HF, and they are indeed a patient with a reduced ejection fraction type of HF, they were admitted for CHF (meaning then they would be classified as stage C heart failure), and they were at least NYHA class II, then I would say that yes, that's probably a good patient to be on that medication and. You should continue them on that medicine, if it is affordable for them.

In terms of when to titrate the medicine, typically in an outpatient setting I titrate that medication every 2 weeks. If I have a patient, for example, who shows up to my clinic very hypertensive yet they are on that medicine, or maybe on a very aggressive antihypertensive regimen, I might shorten that next up-titration to 1 week. I will ask them to measure their blood pressures for a week or have them come in to the office and visit my nurse and get a blood pressure check after 1 week and make that up-titration sooner because it's not good for a patient with HF to be chronically hypertensive.

Dr Gowani: When the patient comes in, after they have been on this medication for a week or 2 weeks, and has been stable while titrating them, I'm asking about their blood pressure and evaluating it, looking at their chemistries to see how their kidney function is

tolerating it, is that correct? And then I am asking them about potential side effect-type symptoms like facial swelling or cough.

Dr Rouf: The symptoms patients get most frequently when starting the medication are hypotension, the low blood pressure, lightheadedness, and dizziness. Compared to other drugs they may have been used to, such as ACE inhibitors or ARBs, this drug has a greater potential to drop the blood pressure very significantly. So I am very careful in asking about lightheadedness and dizziness, and then probing further about whether it is a fleeting lightheadedness or dizziness on position. I ask if they are concerned about falling. If they tell me that they are concerned about any of those things, then we back off on the medication. Whether that means we stop the medicine depends on how symptomatic the patient is. So those are important considerations. You do want to always ask any patient who is on an ACE inhibitor, an ARB, or an angiotensin receptor-neprilysin inhibitor (ARNi) – which is the class of medicines this is – whether they have cough or any tickling in their throat or facial swelling, as that can happen with any 3 of those medicines at any time during the course of their treatment.

Dr Gowani: And with the effect on blood pressure, should I anticipate that might happen? Do you ever make any corresponding changes before you evaluate the patient? For example, when you start sacubitril/valsartan do you go down on another antihypertensive the patient might be on, or do you wait and see the effect as long as the patient has a safe amount of blood pressure room and then evaluate them 1 or 2 weeks after?

Dr Rouf: It depends on the blood pressure that we start with. If someone has a robust systolic blood pressure – say systolic in the 120s – then I feel very comfortable in making the switch directly from an ACE inhibitor or an ARB to that medication without down-titrating any other medication. If they're a little bit more soft – say systolic in the 100s – the trials actually excluded any patients who had a systolic blood pressure less than 100. So if they're in that sort of a marginal range I might consider, for example, going down on their carvedilol in order to get them on the lowest dose of sacubitril/valsartan.

I would say for an internist that if you have a robust blood pressure of a systolic of 120 or above, you should feel comfortable with making a switch. If you have something on the softer side, meaning a systolic in the range of 100 to 110, that might be an opportunity to refer to a cardiologist for initiation of the medication.

Dr Gowani: The medicine has some natriuretic effects. Can you just talk about how you see how it changes your diuretic dosing sometimes?

Dr Rouf: It does actually. So it is a natriuretic so it will make patients urinate more frequently. I do commonly see that when I place patients on this medicine, they will need a lower dose of their diuretic, if they are on one. This is another reason to monitor kidney function at every up-titration of the medicine so to make sure that they're not too dry.

Dr Gowani: For patients of mine who do not have a cardiologists within our medical system, how do you recommend that communication be made? If I'm starting a patient with HF on sacubitril/valsartan, I would want my cardiologist to know.

Dr Rouf: Yes. This may be the biggest challenge with regard to getting patients who have HF on this medicine. HF is a growing epidemic nationwide, and these patients are not going to necessarily have the luxury of access to a cardiologist, at least in a timely way or even have access to an HF physician for that matter.

I do think it's important for internists and primary care physicians to have this drug in their arsenal, and that if they feel comfortable starting their patients on the medicine, they do so if that patient can afford it. There are online resources that help you to figure out what the cost would be to your patient, and you can enlist staff in your office to facilitate figuring out the cost and managing the prior authorization paperwork to get that patient onto the medicine. A vigilant internist should also understand whether his or her patient has the cognitive ability and understanding of what to do when switching medications, particularly from an ACE inhibitor to this drug.

Dr Gowani: So to summarize my approach to starting a patient with CHF with reduced ejection fraction on sacubitril/valsartan, I would identify that this is the right patient, that they have had CHF, that they have reduced ejection fraction, that they're comfortable with their medications and their medical literacy, that we have at least reached out to their pharmacy in some way to see if they can afford the medication, and that they don't have any prohibitive side effects such as angioedema to prior medications that would make me not want to start it on this particular patient.

Once that happens I would explain that this is an alternative medication to an ACE inhibitor or an ARB and then once we confirm that the medication is affordable, I'd have a person from my staff, or myself, call the patient to reconfirm that they know exactly when they're going to stop their ACE inhibitor. Then, 48 hours later, the patient would be instructed to start the sacubitril/valsartan. If they're on an ARB, they should discontinue the ARB, stop for one day, and then the following day start the sacubitril/valsartan. After that, every 1 to 2 weeks depending on my concern for their blood pressure I would follow-up with them in the clinic and do a blood pressure check, make sure that they are not having an excessive diuretic effect or high blood pressure effect from the medication, while I'm also evaluating for things like angioedema, facial swelling, and cough. Finally once they have been titrated to a dose that was used on the trials …

Dr Rouf: …yes, the target dose was 97 mg/103 mg. A peculiar aspect of this combination drug is that they are weird doses. For sacubitril/valsartan, I believe the lowest dose is 24 mg/26 mg, the next dose is 49 mg/51 mg, and the next dose after that is 97 mg/103 mg. We are trying to work them to get to that highest dose of the medication as that is the target dose that was deemed to be effective in reducing hospitalizations and mortality in PARADIGM.

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