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Recurrence of Cushing's and the Changing Landscape of Medical Management

Announcer:
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Dr. Fleseriu:
It's critical that clinicians have an accurate picture of recurrence to properly monitor their patients with Cushing's disease. Today, we'll discuss the complexity involved in the diagnosis of Cushing's so that recurrence is detected as soon as possible.

This is CME on ReachMD, and I'm Dr. Maria Fleseriu.

Dr. Auchus:
And I'm Rich Auchus.

Dr. Fleseriu:
Let's dive right in. Rich, what is recurrence, and how do we monitor for it?

Dr. Auchus:
Well, since we're talking about Cushing's disease today, which is hypercortisolemia due to an ACTH-producing pituitary tumor, that means regrowth of the tumor in a sufficient amount to cause hypercortisolemia that can be clinically manifest. Now the recurrence rates are surprisingly high, probably about 50% overall in all-comers. It depends on whether it was a macroadenoma or microadenoma; recurrence is more frequent with macroadenomas. Depends on the surgeon who did the surgery, less frequent in a good surgical center. But basically, we have to document the recurrence of the hypercortisolemia by some biochemical measurement. Often, the patients know when their Cushing's come back because they know those symptoms, whether it be sleep problems, weight gain, or problems with their blood pressure control or their glucose control.

So like in diagnosing Cushing's in the first place, we have the usual repertoire of testing, the late-night saliva cortisol, the urinary free cortisol, and the dexamethasone suppression test. And in this case, there are several studies that have shown that the late-night saliva cortisol is the most sensitive measure because it really picks up that first beginning when the nocturnal cortisol excursions remain high before urinary free cortisol is elevated and before many people fail the dexamethasone suppression test. And I would say that there's early recurrence, people who did not have an adequate surgery, that accounts for maybe 20% of people. Then there's middle recurrence when people recur between 1 and 5 years and then late recurrence when people recur after 5 years. And I think, in total, it's going to be about 50%.

Dr. Fleseriu:
I totally agree. The diagnosis of recurrence also depends, in my view, in which were the tests that were abnormal to begin with. But late-night salivary cortisol is definitely the first one to be abnormal in the large majority of patients.

So for treatment of Cushing's disease, most patients will require surgery; we know that. But, Rich, I want to hear from you. What can you tell us about medical therapy, and how do you tailor the treatment for our patients?

Dr. Auchus:
Now we're fortunate that there are several drugs that are available to us. So again, it would depend on the patient characteristics. What are their comorbidities, what is their age, their sex, their future perspectives, how much surgery have they had, how severe is their disease, and what side effects of the drugs do we want to avoid and what positive additional effects of the drug do we particularly want to take advantage of?

So I'm going to kind of go through the categories. We have the cortisol receptor antagonists, and currently, the only one available is mifepristone. This is approved for treatment of hypercortisolemia of any type with hyperglycemia. And I think, you know, the evidence that we have from the SEISMIC trial is that the hyperglycemia really does improve quickly and dramatically with this drug. Of course, the patient characteristics that were in that study were people who had really bad disease and really bad comorbidities, so they were coming from a high level. And I don't think the other drugs have been really compared in such a severely affected cohort. But it really does work very well for the hyperglycemia and weight loss and parameters like that.

Then there's tumor-directed drugs: pasireotide, both the subcutaneous form and the long-acting form. Now the good thing is that it is tumor-directed, and so the long-term studies of this agent and its different preparations have shown that there can be some regression of tumors.

This is particularly useful in people with macroadenomas. But the negative part of pasireotide is that it also binds to the receptors that are on the beta cell, so it causes hyperglycemia. So it's sort of the opposite of mifepristone, if you will, that hyperglycemia often gets worse, but there is tumor-directed effects in long-term use. I think most people now would only use the subcutaneous in short term in preparation for using the long-acting drug.

Then the cortisol synthesis inhibitors osilodrostat and levoketoconazole. So osilodrostat is sort of the new metyrapone. It's a very potent 11-hydoxylase inhibitor and there are now several studies both in the registration trials and other studies that were in compassionate use or expanded access that have shown very reliable reductions in cortisol production as measured by urinary free cortisol, sustained control, failure to escape from treatment. Most people that are controlled remain in control for a long, long time. Somewhere between 60% and 80% normalization of urinary free cortisol across all these studies, including some investigator studies that use people with very severe disease. And then, there's levoketoconazole, which inhibits several enzymes, in particular the 17-hydroxylase enzyme. About 30% to 60% control, I would say, overall, in the studies that have looked at it. And also very effective in controlling androgen synthesis, which is useful for women, particularly those who are bothered by hirsutism.

So those are the main options that we have now. So we have not only several different agents, but several different mechanisms of action as well.

Dr. Fleseriu:
Thank you. Great overview. So you touched briefly, but how do we select one drug versus the other? Can you comment on the long-term data? There are several studies for adrenal steroidogenesis inhibitors, in particular long term, but also for pasireotide, that you briefly mentioned.

Dr. Auchus:
Right. So I think with levoketoconazole, again, 30% to 60% long-term success. You have to think about what the unique pros and the unique cons are. So I think, just like ketoconazole, there is the potential for liver enzyme elevation, transaminase elevation, as well as QT prolongation. The drug needs to be taken on an empty stomach. But it has the benefit of also lowering androgens. So, again, I think somebody who, where hyperglycemia is not a terribly prominent issue, who has androgen excess that needs to be controlled, that has moderate Cushing's, this is a good choice. The drug is taken twice a day, but they have to take it without a proton pump inhibitor.

Osilodrostat from the LINC 2 and LINC 3 studies, and the LINC 4 study as well, you know, 60% to 80% success rates in controlling urinary free cortisol. Outcomes seem to be better if you also control the late-night saliva cortisol in these people. Now what can happen is that because of the site of the blockade, that mineralocorticoids and androgens can accumulate. It turned out not to be that much in the trial. About 7% of patients had worsening in hypertension and hypokalemia, but other people improved. And androgen excess didn't seem to progress in these people. We can talk later about why that might be.

Now pasireotide, I think, is also about 30% to 60%, maybe a little bit higher in the long-term trials. But again, with long-term studies some slight shrinkage of tumor seen in a substantial number of patients. But again, hyperglycemia is the main reason for discontinuation of that drug. You know, mifepristone hasn't really had long-term studies published on it. But, you know, I think we all

have a couple of people that have been in it for many years.

So those are the main considerations. You know, what are the unique pros and cons of each drug, how long does it take to get control, how carefully do you need to monitor people for potential adverse events, and what do they really need from a clinical perspective of what parameters/comorbidities of the disease do they really need improvement with.

Dr. Fleseriu:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Maria Fleseriu, and here with me today is Dr. Richard Auchus. We're discussing recurrence in Cushing's disease, as well as selecting medical therapy.

This makes a perfect switch to our next topic. But first, I wanted to really highlight the fact that having long-term data, especially in prospective studies, helps us tremendously, not just for safety, but also for efficacy. In some of the LINC trials we had over 5 years, and in LINC 3 we had, for example, over 100 patients that were followed. And we noticed that the dose requirements are lower over time. So this is very important also, that the dose is coming down, as you briefly mentioned. So I think having prospective data is really helping.

And switching now from efficacy to adverse events, you talked about how you select the treatment a little bit based on efficacy, but you're talking about adverse events. But how do you monitor for all these adverse events for the medication that you are talking? And then, the most important thing is, how do you know it's adrenal insufficiency or glucocorticoid withdrawal syndrome, I think the toughest question of all.

Dr. Auchus:
So with Cushing's, I always say you have to keep one eye on each of 3 or 4 different things. And so you have to monitor the underlying disease process, right? So periodically, you need to reimage the pituitary; you need to remeasure ACTH. Even on cortisol synthesis inhibitors, once people get into a steady state and glucocorticoid receptor antagonists, their ACTH should remain stable. And if it's starting to change, then you have to worry that the disease is progressing.

Then, you know, hyperglycemia is one thing that we can monitor quickly. So, again, some drugs like mifepristone or osilodrostat, where you're going to get rapid improvements, you will want to cut the dose of insulin as you start treatment. Whereas other drugs, like pasireotide, where you make it worse if people are not treated, you're going to need to monitor that in the short term.

Potassium is something that could go up or down depending on the mechanism of action and the severity of the disease. So electrolytes, basic panel drugs that can cause QT prolongation, particularly in people at risk, particularly if they're on other drugs, EKG in the near future. So I think your goal is not to immediately normalize the urinary free cortisol. You want to start people on low doses to avoid adverse events and to dial in the treatment slowly. This will also mitigate the potential for glucocorticoid withdrawal symptoms. So I titrate medications primarily to withdrawal symptoms. So if someone has recurrent Cushing's and I bottom them out, I know they're going to say, I can't take this medicine. I hurt all over; I'm tired all the time. So I try to give them a low dose, watch it improve, because any dose you give them will help them in the short term, right? So avoid side effects by starting modest doses, monitoring glucose, potassium, blood pressure, EKG, liver enzymes, and then slowly going up on the dose as people tolerate them.

Dr. Fleseriu:
Yeah. This is very hard and you're right. I think we're juggling at least 5 things, not even 4, because we also have to look at MRIs from time to time, especially for drugs that are not working at the pituitary level, and if the patients have macroadenomas. And otherwise, the glucocorticoid withdrawal syndrome is fascinating, and the patients are reaching it at different doses. And it's not just how much you decrease. We used to think that if they're very high and you decrease to normal, they will have it, but sometimes, minimal decreases can make patients' life way more complicated, and I usually dial back the dose. And I start, I have to say, with adrenal insufficiency. I also start lower doses, as you said, and then go up slowly.

Dr. Auchus:
And it's going to be a lot worse if you make them adrenal insufficient or cause them some side effect that's going to make them reluctant to take the medicine. I think the most important thing is to warn people that it is going to happen. I mean, this is what I tell them before the surgery, is that you're going to feel worse before you feel better. And the same thing is true with the medication. You've got to tell them you will get these withdrawal symptoms. I am going to try to dose you slowly to minimize it, but it still might happen.

That is the single most important thing you can do when you start treatment is preparing people for what's going to happen.

Dr. Fleseriu:
Well, this has been certainly a fascinating conversation, but before we wrap up, Rich, can you share your 1 take-home message with our audience – not 5, 1.

Dr. Auchus:

I would say take your time titrating any medication you use.

Dr. Fleseriu:
And my 1 final take-home message, though, as a chair, I should have 2, is individualized treatment is probably the most important. One drug might work better for a patient than the other drug. And again, start slow and monitor the patients very closely and they are well prepared in what to expect.

That's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Richard Auchus, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Auchus:
Maria, it's always fun talking with you. You are a wealth of information.

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