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## Cushing's Disease: From Diagnosis to Treatment Selection

### Announcer:

Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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### Dr. Fleseriu:

This is CME on ReachMD, and I'm Dr. Maria Fleseriu. And here with me today is Dr. Richard Auchus.

Let's dive into a case, Rich. We have a 41-year-old woman who has been diagnosed with a mild Cushing's disease. She has a 2-cm pituitary macroadenoma, and as we expected, failed pituitary surgery, but she still has a large residual tumor. Her potassium is normal. She's on medication for prediabetes and hypertension. No plans for pregnancy. Which medication you think would benefit this patient?

### Dr. Auchus:

Yeah, so this is a tough case. She has a large tumor, so it's not surprising, as you said, that she has residual disease. And so the first thing that I think about is whether she needs tumor-directed therapy. And so that would be something like pasireotide. Now the pros of pasireotide is, again, that it is tumor directed, and it's not a bad choice for someone with mild to moderate Cushing's, but it can make hyperglycemia worse. And if she has prediabetes, it could actually make her require treatment for her diabetes. So a little pro/con there.

If I was more worried about the hyperglycemia, then mifepristone might be a good option because it does a very good job at controlling the hyperglycemia. But it's not tumor directed, and because it blocks the glucocorticoid receptor, the ACTH can go up, and it can make hypokalemia worse and hypertension worse as a result of extra cortisol being made. There's not a lot of evidence that it increases the growth of tumors, but we worry that by not treating the tumor directly, that there can be progression of the tumor.

So I think in both of those cases, there are some pros but some con, and I'd be interested in hearing what your thoughts are about steroidogenesis inhibitors in this patient.

### Dr. Fleseriu:

Thank you, Rich. Probably, I agree with you. I would start this patient first on a tumor-directed drug, pasireotide, that works in half of the patients with mild disease, definitely not more unless we had combination. Cabergoline might be an option, especially for combination.

But we have now 2 approved adrenal steroidogenesis inhibitors, osilodrostat and levoketoconazole. Osilodrostat is very potent. It works relatively fast. And we have long-term data now that, yes, some patients had increase in tumor; some patient had decrease in tumor. And we don't really know if it's natural progression of the disease, but we always worry. So at some point, if I see tumor growth on medical therapy, this would be a patient with a residual tumor that I will recommend radiation.

We have data both for osilodrostat and also for levoketonazole of improvement of glucose and also improvement in blood pressure. The key is not in all patients. So the large majority will improve. But this is the key for individualized treatment; we have to see. And then of course, with a potent adrenal steroidogenesis inhibitor, we might see more adrenal insufficiency. The patients can have more withdrawal than we see, for example, with pasireotide.

So once patients are on treatment, depending on the treatment they are on, they have to have very close monitoring. We usually use visits with telemedicine in between. It's a risk of adrenal insufficiency with all the drugs that you had mentioned and I had mentioned, and then also glucocorticoid withdrawal syndrome, and then sometimes it's hard to differentiate between them.

But the most important thing would be the patient has a tumor that's residual; the patient has Cushing's so we need treatment. So which treatment to start with? That really depends what the patient prefers. A drug that works at the pituitary level would be great for us, but sometimes the patients want an oral medication and not an injectable. And then we'll start with a steroidogenesis inhibitor, and I give the patient the data about potency, and some want more hirsutism control, for example, at the beginning, that we can't get with levoketoconazole; longer term, this is not an issue for osilodrostat.

So do you have any key points that you want to talk about, Rich?

**Dr. Auchus:**

Well, I think that there is no perfect drug. They all have their pros and cons, and when you're trying to decide what to start with, think about what are the most important parameters for that particular patient that you want to control and the one drug that is least likely to cause exacerbation of comorbidities. And then, as you said, that oftentimes you have to give it a try. Start low, advance the dose slowly, and then you may have to shift gears if it's not as efficacious as you would like it to be.

**Dr. Fleseriu:**

Well, this has been a great discussion, a great bite-sized case. And thanks everybody for tuning in.

**Announcer:**

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