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Personalizing Treatment in Cushing's Disease

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Personalizing Treatment in Cushing's Disease" is provided by Prova Education.

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Dr. Fleseriu:
Are you prepared to navigate the many challenges of Cushing's disease, focusing on assessing therapeutic response, patient selection and personalized approaches, including counseling on timing and speed of recovery, as well as symptoms burden?

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

Dr. Bancos:
And I am Dr. Irina Bancos.

Dr. Fleseriu:
Irina, can you set the stage for us with some background information on Cushing's disease and the burden it puts on our patients?

Dr. Bancos:
Yes, of course. Well, that's a lot to discuss.

I would like to start by outlining that symptoms and signs of Cushing's disease result directly from chronic exposure to cortical excess. But these symptoms and signs are very nonspecific. And there are many reasons for that. The symptoms and signs could be mild. They could be seen in many other disorders and are in general common. For example, weight gain is a common symptom. Weight gain and Cushing syndrome or Cushing's disease is especially in the abdominal area. But this is common otherwise. People complain of fatigue, complain of muscle mass loss and weakness. Women have menstrual abnormalities. There are quite a few metabolic abnormalities that happen in Cushing's disease: development of diabetes or prediabetes, cholesterol issues, high blood pressure, osteoporosis, and fractures. Patients with Cushing's disease are also at high risk for clots, DVTs [deep vein thrombosis], or PEs or pulmonary embol. Patients with Cushing's also have a high predisposition to infections, especially fungal infections. And on physical exam, we may see supraclavicular pads, dorsocervical pads, and skin changes such as striae, easy bruising, and thinning of the skin.

Dr. Fleseriu:
Thank you, Irina. So it's a complex of factors that we're looking for, including the comorbidities that you nicely mentioned earlier, to guide our selection for treatment, both for first-line, and furthermore, for secondary adjuvant treatment.

Dr. Bancos:
Absolutely agree. And I think it's important also to note that even in the best hands, pituitary surgery may not result in cure in around 30% of patients are so. It's also crucial to remember that surgery is not the only option for our patients with Cushing's disease.

Maria, what can you tell us about adjuvant treatment, such as medical management, and the goals of that therapy?

Dr. Fleseriu:
So adjuvant treatment consists in sometimes more than one method. So medical management has moved from one of the options we have available for these patients to being now really the mainstay of adjuvant treatment. We're so pleased that for the last 10 years, we had 4 drugs approved in the US by the FDA, starting in 2012 with mifepristone, a glucocorticoid receptor blocker approved for hyperglycemia associated with Cushing's Syndrome. The same year was approved pasireotide sub-q, and then later on a few years later, pasireotide LAR a somatostatin receptor ligand that works at the pituitary level, the first drug that actually works at tumor level and also decreases the ACTH. And we'll talk later about the efficacy and differences between drugs. After that, the osilodrostat was approved in 2020. This is an adrenal steroidogenesis inhibitor that blocks the 11 beta-hydroxylase and also blocks the aldosterone synthase. It's a very potent drug. And then a year later, in 2021, levoketoconazole has been approved. And this is the stereoisomer of ketoconazole. So we have many drugs approved.

And then keep in mind that we also have several other drugs that we have been using for years including ketoconazole, metyrapone, mitotane, etomidate, cabergoline. They are off label in US. Ketoconazole and metyrapone are approved, for example, in Europe and other countries. So we have now a corollary of methods, even from medical point of view.

Now how to choose one versus the other. It's also a personalized decision, and patient preference should play a role. Several of these medications are oral medications; a few are injectable.

For the medication that we're using day to day, osilodrostat is the most potent one we have available. Several long-term prospective studies have shown that up to 77% of patients in the most recent study have been controlled, and this one was controlling with placebo, for example. And then even longer term, up to 67% of patients could be controlled. And last week we have published that we have patients controlled for over 6 years. So this is a – a drug that has been prospectively studied. And it's very potent, of course, and works rapidly.

We have to think also about adverse events. So the most frequent adverse event was related to adrenal insufficiency. All of the potent drugs can decrease the cortisol too much. And sometimes it's not even adrenal insufficiency. I'm curious to hear from you soon about what we differentiate between adrenal insufficiency and glucocorticoid withdrawal syndrome, for example, but we have to keep in mind and how we speed up and titrate the drug is very important.

For levoketoconazole, we're also starting with a lower dose and increase and titrate up. This is how we usually do for all the drugs for Cushing's. Very important, levoketoconazole has some warnings for QT prolongation and liver function. So we have to closely follow up that. And then for pasireotide, for example, that works very well at the tumor level for some patients that have tumor presence, we know from the beginning that even in mild Cushing's is going to respond in 50% of patients maximum. So we have to set up our expectations for controlling our mind. But the hyperglycemia is also very frequent; up to 69% of patients can develop hyperglycemia.

With all the medications for Cushing's that I have described, and I focused just on the FDA-approved now, we should see clinical improvement, in addition to looking at numbers. So efficacy, based on cortisol, as I mentioned earlier, for most drugs, with the exception of mifepristone, it should be assessed in combination with clinical improvement, clinical features, several of the one you mentioned earlier, but also comorbidities.

For those just tuning in, you're listening to CME on Reach MD. I'm Dr. Maria Fleseriu, and here with me today is Dr. Irina Bancos, and we're discussing strategies to personalize treatment for patients with Cushing's disease.

Dr. Bancos:
Thank you, Maria. I do have a question about the use of cortisol measurements in following patients for recurrent Cushing disease and also during medical therapy. For example, after a curative pituitary surgery, I would use 24-hour urine cortisol measurements in my patients with Cushing's to diagnose a potential recurrence. Do you use cortisol measurements in your patients treated with medical therapy?

Dr. Fleseriu:
Thank you, Irina. The medical management option is even more complicated to follow than surgery, but also once the patients are closely observed, the outcomes are clearly improved. So for example, in patients that are on medical therapy, with the exception of mifepristone, I do serial urinary free cortisol and look to see if they are decreasing, the speed of decrease; sometimes I do more than one. But I also check the salivary cortisol. And there are data showing that if patients are controlled both with urinary free cortisol and salivary cortisol, their clinical outcomes are actually better. So this is very interesting, because in the initial studies, we all look at urinary free cortisol as endpoint. So it's a little bit hard to detect which one would be more important, but if somebody's asking me, I would say both. We should try to really normalize the circadian rhythm. This is not always possible. But if the patient has normal urinary free cortisol and the saliva cortisol is still abnormal but they have clinical improvement, so I'm not thinking of switching to another treatment,

then definitely I would up-titrate the dose and I will up-titrate the evening dose to try to improve this diurnal variation. So I do urinary free cortisol in everybody. I do salivary cortisol in everybody. Again, this excludes the glucocorticoid receptor blockers where we can measure cortisol. And then I use the measurement of the morning cortisol, not to tell me where we are from Cushing's point of view, but just to make sure that the patients do not have adrenal insufficiency.

So this goes back to the individualized treatment. What do we need to do for our patients? And we look for recurrence. The salivary cortisol can sometimes be abnormal a year before the urinary free cortisol, so this one pattern. And then for medication, also depends on the comorbidities. Sometimes salivary cortisol could be falsely elevated for uncontrolled diabetes or hypertension, and has been shown. So it's really important to look at numbers, but not look just at numbers. The clinical pictures should play a very important role.

So can you tell us a little bit more, Irina, with all these options, how do you select the right therapy for our patients? And once selected, how do you go from there?

Dr. Bancos:
Wow, that's a great question. And you actually answered or touched upon several of the things. So let me recall together with you that you've mentioned that some of our patients are just too sick to have surgery when we see them first.

So one of the factor is, how ready is my patient to have a curative or potentially curative surgery? So sometimes we would wait a bit or treat with medical therapy before our patient is ready to undergo a potentially curative surgery.

The other factor that I think is important to consider is availability of experienced pituitary surgeons or availability of early surgery. It's sometimes, in different environments, patients have to wait for months to have a curative surgery. And we would not recommend delaying treatment of Cushing's until, with or without anything else, until that surgery can occur.

The third factor would be patients' preference. In my opinion, patients would need to hear about all the options available to them and participate in that individualized discussion on how they would like to approach their Cushing disease.

So how do we distinguish or differentiate between different therapies? As you recall, the mainstay of Cushing's disease as far as management would be pituitary surgery. But sometimes it's already clear based on the initial imaging that pituitary surgery would not be curative, for example, with some of the more invasive pituitary tumors. In that case, we would be planning additional therapies after potential debulking therapy, such as radiation therapy that Maria mentioned earlier, and medical therapy. In times when pituitary surgery, radiation therapy, and medical therapy are not an option, we would consider also bilateral adrenalectomy in selected patients.

I would like to talk a little bit more about glucocorticoid withdrawal syndrome, because this occurs both after a curative surgery, let's say pituitary surgery, but also during medical therapy. What is glucocorticoid withdrawal syndrome? It's frequently confused with adrenal insufficiency because there is quite a bit of overlap in symptoms. For example, glucocorticoid withdrawal and adrenal insufficiency both present with a lot of fatigue, a lot of body aches and pain, a lot of similar exacerbation in anxiety and depression. Nausea is also a common overlapping symptom in glucocorticoid withdrawal syndrome and adrenal insufficiency.

Let me define glucocorticoid withdrawal syndrome. This is a body's reaction to withdrawing from supraphysiological cortisol levels. I usually like giving an example of drinking too much coffee. If a person drinks 5 cups of coffee a day, it would be quite difficult to go from 5 cups of coffee a day to 1 cup of coffee a day. That person would feel unwell and tired and will probably have a headache and sleep more. So if we make a parallel to cortisol, going from 5, 10 times abnormal, higher than normal cortisol levels to normal cortisol levels after surgery would not feel well. And unfortunately, the symptoms are very long. So at least it feels this way. They sometimes last 3 months, sometimes 6 months.

Dr. Fleseriu:
And I think that the glucocorticoid withdrawal syndrome diagnosis is very hard. After surgery, sometimes we know that the decrease is very abrupt, so we expect it. But with medication, could be seen months later after, for example, we up-titrate the dose. So I think especially with potent drugs, as I mentioned earlier, as osilodrostat, but also in levoketoconazole and pasireotide and mifepristone, we see the patients having symptoms that could be withdrawal or could be adrenal insufficiency. So in my mind, I want to make sure the patient doesn't have adrenal insufficiency. So definitely I measure a cortisol in the morning unless the patient is on mifepristone when we make the decision on clinical diagnosis. And if I think it's adrenal insufficiency, I will stop the drug for Cushing's and then decide, if symptoms are not resolving, to give hydrocortisone. All my patients with Cushing's have some treatment at home for adrenal insufficiency.

Now, if by any chance the symptoms are resolving with decreasing the drug, we're back to square one. Is this that we up-titrated much faster than we should? Or is this really adrenal insufficiency? And we have shown in studies, for example, for osilodrostat, that if we up-titrated much slower, like it was in LINC 4 versus LINC 3, the rates of adrenal insufficiencies were lower. So in my mind, this made

me change a little bit of the clinical practice in I used to see a high cortisol, I would go to a higher dose because, you know, patients have been missed for so many years. I would want the patients controlled very fast. However, for a lot of patients, would be better to slowly up-titrate so they can tolerate better. As you mentioned, I would not like to go down from 5 to 1 cup of coffee. I still like my 3 cup of coffees.

Dr. Bancos:
Thank you, Maria. And it really sounds like it's art in management.

Dr. Fleseriu:
I think patients with Cushing's disease and Cushing syndrome are fascinating, and we should all make all the effort to really individualize therapy, as we mentioned earlier.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank you, Irina, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Bancos:
It was always a pleasure. Thank you.

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