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Normalizing mUFC in Cushing's Disease

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Dr. Mencia:
A significant number of patients with Cushing's Disease will require medical therapy, either after surgery or in lieu of surgery. One of the most challenging aspects of care can be normalizing the concentration of mean urinary free cortisol, or mUFC. So how do we overcome that challenge and decide what options are best for our patients when trying to achieve disease control?

This is CME on ReachMD, and I'm Dr. William Mencia. And here with me today to help answer these questions is Dr. Eliza Geer. Welcome.

Dr. Geer:
Thank you for having me. It's great to be here.

Dr. Mencia:
Well, let's dive right in, Dr. Geer. Can you review the medical management goals for patients with Cushing's disease?

Dr. Geer:
Sure. So the goals of medical management for Cushing's are really, you know, primarily to normalize cortisol levels, but also to reduce or eliminate the associated comorbidities, physical features, and symptoms. These include hypertension, glucose intolerance, obesity, mood and sleep changes, just to name a few things. And ultimately, we really, you know, want to improve our patients' quality of life by reducing symptom burden.

I will also add that, you know, for patients with significant tumor burden, another goal is to maintain tumor control. But medical therapy is needed for a lot of patients, for patients who have persistent or recurrent disease after surgery or for those who are poor surgical candidates. But before we proceed with medical therapy, we really need to consider the risks/benefits of the medical therapy we're considering versus, you know, possibly another surgery, radiation therapy, or adrenalectomy.

In terms of assessing treatment response to medical therapy, one of the main ways we assess cortisol normalization is by the 24-hour urine cortisol level, and most clinical trials use this as the primary outcome to assess success of therapy. So the advantage of the 24-hour UFC is that, at least in theory, it reflects the integrated cortisol production over a 24-hour period.

Another way is a late-night salivary cortisol value and that's also very important, because we know that loss of the circadian rhythm of cortisol with abnormally elevated levels at night is one of the ways we establish the diagnosis initially. But unfortunately, cortisol circadian rhythm is not always restored with medical therapy.

Dr. Mencia:

Thank you for that, Dr. Geer.

And it certainly sounds like there is a lot of variability in terms of how we monitor the disease, but I'm sure there's also variability in how we treat, especially when we consider how there are several different classes of therapy that can be used in Cushing's. How do these classes differ, and how do you decide what is best for your patient?

Dr. Geer:
So we have a number of medical therapies now to consider. So for our tumor-directed therapies, we have cabergoline and pasireotide. Cabergoline is a dopamine receptor agonist. Of course, we use this very commonly for prolactinomas. But it's also used for Cushing's disease since corticotrope tumors also express dopamine receptors. Pasireotide is a second-generation somatostatin receptor ligand. It binds 4 of the 5 somatostatin receptor subtypes and has particular affinity to the fifth somatostatin receptor.

For adrenal steroidogenesis inhibitors, we have some that had been available and in use for many years. That includes ketoconazole, metyrapone, and we have others that are more recently studied, including levoketoconazole and osilodrostat.

So levoketoconazole is the enantiomer form of the racemic mixture of ketoconazole. So these 2 therapies have the same mechanism of action. Ketoconazole is an antifungal medication that's been used off-label for many years to treat Cushing's syndrome, and levoketoconazole is an investigational therapy. Both of these therapies act on multiple enzymes in the cortisol synthesis pathway, including the cholesterol side-chain cleavage, 17-alpha-hydroxylase, and 11-beta-hydroxylase.

So metyrapone and osilodrostat similarly can be grouped together, since they both act on the same enzyme, 11-beta-hydroxylase, and that catalyzes the final step in cortisol synthesis. And osilodrostat is a potent cortisol synthesis inhibitor, it's taken twice daily rather than 3-times-daily administration need for metyrapone due to the longer half-life, and it was FDA-approved for the treatment of Cushing's disease in March of 2020 after completion of the first phase 3 trial, the LINC 3 study, which I can discuss more later.

And so in terms of our glucocorticoid receptor blockers, we have mifepristone and relacorilant. Mifepristone is also known as RU-486. It blocks the glucocorticoid and the progesterone receptor, and it was approved for the treatment of hyperglycemia from Cushing's in 2012. Relacorilant is a sort of second-generation GR antagonist. It's investigational; it's currently being studied in a phase 3 trial. And it's more selective for the GR, so it doesn't have any action on the progesterone receptor.

Dr. Mencia:
So that certainly is a lot to keep in mind. You mentioned that some of these therapies have been around for some time and that others have been approved much more recently. And we also know that there have been multiple clinical trials that have been reading out data. Recently, you mentioned one, the LINC 3, from which there was an approval, but we also have the LINC 4, PROMPT, and other trials. What have we learned from these?

Dr. Geer:
Sure. Just for thoroughness sake, I want to also include cabergoline and pasireotide to start out with, which are tumor-directed therapies. For cabergoline, we don't have any systematic trial data for this therapy, but there have been several small observational studies, typically using low-dose ranges, about 2 mg per week, and showing overall a response rate of 25% to 40%. Unfortunately, some patients do lose response to this therapy, either from treatment escape or intolerance, and that's seen in about 40% of patients.

And so our second tumor-directed therapy is pasireotide, which is an approved therapy for Cushing's, and that was approved in 2012 after completion in the phase 3 trial that was published in *The New England Journal of Medicine* that year, and it randomized people with Cushing's disease to 2 doses of the short-acting form of pasireotide. And they found that the people who got the higher dose, the 900 mcg twice a day, 25% of them achieved a normal UFC. They also found that there were clinical improvements including improvements in blood pressure and weight. And the advantage of a tumor-directed therapy is the potential to reduce tumor size.

So moving on to more recent data for metyrapone, the first prospective trial was completed; this is the PROMPT trial that you mentioned. And that was presented, it hasn't been published in publication yet, but it was presented at ENDO this year. So this was a single-arm, open-label study. It included 50 patients with Cushing's syndrome of any etiology and showed that with a median final dose of 1,500 mg per day, 47% of the cohort achieved a normal UFC. They also found that there are clinical improvements including improvements in cholesterol, hemoglobin A1C, and blood pressure. And in terms of adverse events, there was reversible adrenal insufficiency in 12% of the patients.

So moving on to osilodrostat, this is our final cortisol synthesis inhibitor that's an approved therapy. Results of the first phase 3 trial on osilodrostat were published in July of last year in *Lancet Diabetes* and *Endocrinology,* and this is the LINC 3 trial. This was a randomized withdrawal trial and it included patients with Cushing's disease. And the primary endpoint was met in this trial with 86% of patients in the osilodrostat arm maintaining a normal UFC after 8 weeks of withdrawal, and that's compared to 29% receiving placebo.

They also found that there were clinical benefits. There were improvements in blood pressure, in weight, in waist circumference, in fasting glucose and A1C, and there were also improvements, importantly, in quality of life and decreases in depression scores. The most common adverse events seen in the LINC 3 trial was adrenal insufficiency, and other symptoms noted were nausea, headache, and fatigue.

There's also the LINC 4 trial; it's a second phase 3 trial that's investigating osilodrostat, and that was presented at ENDO this year. And that showed that the study did meet its primary endpoint, with 77% of the people receiving osilodrostat achieving a normal UFC, compared to 8% of patients receiving placebo. And they also found that there were improvements in quality of life and mood.

Dr. Mencia:
For those just tuning in, you're listening CME on ReachMD. Here with me today is Dr. Eliza Geer, and we are discussing treatment goals and algorithms to the medical management of Cushing's disease.

Dr. Geer, we've certainly reviewed a lot of information so far. You've talked us through the different therapeutic options for medical therapy, the expectations of those therapies, and recent clinical trial data in terms of how we use those therapies. Help us out here a little bit. With all of the different options available and all of the data that you just reviewed, how do you decide what is the best medical therapy for each patient? How do you differentiate?

Dr. Geer:
So it's a great question, you know, treatment of each patient with Cushing's is really an individualized process, and we really need to consider a lot of factors. We need to consider the tumor itself, if they have a pituitary tumor, the size of the tumor, how, you know, is the tumor an aggressive tumor? We need to consider how severely elevated the cortisol levels are and the efficacy of the treatment that we have to normalize the cortisol levels. We need to consider side effects, adverse effects, drug-drug interactions, comorbidities that need to be actively managed like hypertension, hyperglycemia, and other things like patient preferences and cost and availability. If a patient has a large and invasive pituitary tumor, we may favor starting with a tumor-directed therapy like pasireotide or cabergoline.

But some other considerations. One thing that's very important to think about is that since cortisol measurements are really the mainstay of how we monitor medical therapy, clinicians really need to be familiar with the technical issues involved, like the type of assay being used, the range of normal for that assay, and correct collection and timing the assessment. It's very important to educate patients on how to collect 24-hour urine sample accurately, how to do the salivary cortisols, how to do the dex suppression, and the timing of the bloodwork. It's important to note that metyrapone and osilodrostat both can cause significant increases in 11-deoxycortisol, and this can cross-react with some of the amino assays for cortisol and can result in falsely elevated values, which could lead to inappropriate dose titration. So for people taking metyrapone and osilodrostat, if this is an issue, you need to use a structural assay like tandem mass spec and make sure that we don't have that issue with the cross-reactivity.

You know, we need to consider patient comorbidities, so metyrapone and osilodrostat can sometimes exacerbate hypertension and hypokalemia, and this is due to build-up of the mineralocorticoid precursors. This can be treated with spironolactone and potassium replacement, but we do need to check for that. Mifepristone also can potentiate or exacerbate hypertension due to, you know, increased cortisol levels acting on the mineralocorticoid receptor.

Other practical considerations, ketoconazole and levoketoconazole require stomach acidity for absorption, so patients cannot be taking a proton pump inhibitor. There's also a number of drug-drug interactions with a number of the medications. Ketoconazole and levoketoconazole are both strong inhibitors of CYP3A4, so we need to keep that in mind. And of course we need to follow liver enzymes for people on ketoconazole and levoketoconazole. I will mention again that pasireotide can cause hyperglycemia, so this is very relevant for our Cushing's patients who often already have hyperglycemia and that can worsen, and we need to follow that.

And a final note, about osilodrostat is that it's a very potent cortisol synthesis inhibitor. An abstract was just accepted to the upcoming ENEA Conference, this is the European Neuroendocrine Association Conference, so this is hot off the press. And it discusses dosing and titration that was done in the LINC 3 and LINC 4 trials and shows that the more gradual dose increase that was used in LINC 4 compared to LINC 3 didn't delay time to achieve UFC normalization but did result in fewer hypocortisolemia-related side effects. So we think that a gradual dose titration with osilodrostat is very important and that we should titrate this medication really on an individualized basis for the patient to prevent the development of possible adrenal insufficiency.

So it's really a lot to consider. It's imperative to educate patients, their family, their caregivers, about the correct administration of the medications, about potential adverse events, and, importantly, signs and symptoms of adrenal insufficiency and how to assess these if they occur.

Dr. Mencia:
Thank you, Dr. Geer.

Well, this has certainly been a fascinating conversation, but before we wrap up, what is your one take-home message that you'd like to leave with our audience?

Dr. Geer:
I guess I would say that, you know, Cushing's is a very complex condition. It requires multidisciplinary care and often long-term care with management of multiple symptoms and comorbidities. But I really think it's a very exciting time in the Cushing's treatment space. We have a number of recently approved and very effective therapies, and we have additional very promising therapies in development. So I always tell my Cushing's patients that there's always a next step, another treatment or approach that we can try. It's very important to assess patient-reported outcomes, and this will help us to really move the field forward in terms of identifying and developing interventions that really provide symptom control and improve quality of life, in addition to normalizing cortisol values.

Dr. Mencia:
Well, that is certainly great news.

And unfortunately, that is all the time that we have today. I'd like to give a special thank you to our audience for listening in and to you, as well, Dr. Geer, for sharing all of your valuable insights. It was great speaking with you.

Dr. Geer:
Thank you. It was a pleasure talking with you. Thanks for the invitation.

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