Cushing’s Syndrome Treatment Research Highlights: ENDO 2024

Maria Fleseriu

Hello, everyone. We're going to talk today about Cushing's syndrome treatment research highlights from ENDO 2024. I'm Maria Fleseriu, professor of medicine and neurological surgery and director of the Pituitary Center at Oregon Health and Science University in Portland, Oregon, and it's my pleasure to be with you for this CME.

These are my disclosures with funding to the university and scientific consultancy. The learning objectives of this talk are to describe the latest research being presented to better manage individuals with Cushing's syndrome and its clinical relevance and to share new information with their clinical team.

What are Cushing's syndrome and Cushing's disease? They are rare endocrine disorders characterized by chronic hypercortisolism. It's Cushing's syndrome, so everything from endogenous and exogenous. The incidence of endogenous Cushing's syndrome is two to eight per million, but keep in mind that this is probably underdiagnosed. The most frequent type of Cushing's syndrome after the exogenous Cushing's is Cushing's disease. This is a pituitary adenoma producing excessive ACTH leading to hypercortisolism, and the symptoms described on the right, and I'm going to point out some that are very important ones.

And we're talking about symptoms, as you can see, we have clinical features that are more consistent with high cortisol and then also comorbidities, and some are more specific than others. So for example, when we're talking about abnormal weight gain, it's more in the abdominal area and a higher percentage in a short period of time with depression, anxiety, headache, of course, the round place, the muscle weakness is very specific. Women have acne, but also sometimes men. The stretch marks are large and red.

Again, not positive in all patients, but if the patients have them, this is a higher likelihood of the patient having Cushing's. And then bone complications. Many, many patients every year present with long-standing Cushing's and some of them, younger women, had a fracture a few years ago and they didn't have a workup to see why they had that fracture. So this is in general about Cushing's. When we're talking about treatment algorithms, I'm going to focus first on Cushing's disease and then we'll review some other types of treatments too.

So if you look here when we're talking about Cushing's disease, first pituitary surgery, remember it's a tumor in the pituitary. Pituitary surgery is the first line. However, some patients will need preoperative medical therapy first, and then in some patients, pituitary surgery is not feasible. So if they have persistent disease, and you see here in large, then it's getting more complicated. Because if the histology is negative, I always go back and try and figure out if the diagnosis was correct. If the histology is positive, then I move usually to medical therapy. Rarely, if the first surgery was not done in a specialized center, we recommend re-operation, or if the tumor is growing, and then depends on how the patient is doing between medical therapy, radiation, sometimes both and sometimes all of them re-operation, medical therapy and radiation.

What is most important, and I want you to see at the bottom in orange, is once we start a medication, we have to decide if the medication is working. Is the patient-controlled, partial control or no control and then we just have to switch to something else? And if it's partial control, then we will need probably combination therapy or sometimes even switching to another medication. Which medical therapy do we have available? For Cushing's disease, we have three groups, neuromodulators of ACTH release, including pasireotide approved by the FDA and Cabergoline used off-label. And then the other two groups are also used for all types of Cushing's syndrome, adrenal steroidogenesis inhibitors, and you have them here in alphabetical order. However, I wanted to point out that FDA approved are just levoketoconazole and osilodrostat for Cushing's syndrome. And mitotane is approved for adrenal

cancer. The glucocorticoid receptor blockers are approved by the FDA for all patients with Cushing's syndrome and hyperglycemia.

So ENDO's 2024 was in Boston a little bit earlier this year. And there were many, many clinical trials discussed. Real-world studies, some studies on quality of life, comorbidities and many more. Of course, I don't have time to review for you everything, so just go to the abstract and see how interesting was the word of Cushing's and pituitary in general at this ENDO 2024. But I will share with you some important studies and I would like to start with a very interesting study, a real-world impact of Cushing's syndrome, a study done by patients. Unfortunately, the conclusion is that while outcomes have improved over time, patients with Cushing's syndrome continue to report diagnosis delay, confusion about treatment and feeling ignored once the cortisol is normalized. There were 150 questions and as you can see, many, many responses from an international array of countries.

By looking at the results in detail, you can see that from the patient's point of view, we are not doing a great job. Of the patients who are still trying, 75% still trying to determine the new normal. The memory problem that they didn't have before, was 80%. They couldn't go back to work for more than six weeks. This is usually expected. What I was most bothered by was that half thought that the feeling that the medical team was unable to support them beyond cortisol issues. And again, I think this is very important for us as physicians to think about how we can support the patients. Sometimes sending them to other specialties of course. And the results demonstrate the ongoing burden of hypercortisolism I showed you earlier, often starting seven years before an official diagnosis. So overall it's anywhere between 4, 5, 7, but this was... It's true patients could be selective and that's why they answered the surveys because they didn't do well. However, these are very important results.

So let's switch from the quality of life and how the patients perceive that are not doing a great job besides cortisol. In new studies, prospective, retrospective and non-interventional studies with FDA-approved therapies have been reviewed and discussed in detail at ENDO. First pasireotide as you know, it's a multi-ligand somatostatin receptor ligand available either subcutaneously as BID or intramuscular once a month in different doses, approved to treat Cushing's disease in adults for whom surgery was not working or they cannot have surgery due to contraindication. This was a retrospective three-year study, international, run from Europe. And as you can see the design was a little bit more complicated. But you can see highlighted in red the most important things. Some of the patients when they got into the study, this was retrospective, were patients that were new pasireotide users and as you can see the control rate was pretty low overall.

However, if they were prior pasireotide users in the past, that means they responded or partially responded, the control was 67% overall. Then at month 36 the numbers were decreasing for previous users with some dropping overall and less patients. But for new users, the percentages increased. How about Cushing's quality of score? Of course, we know that the blood pressure and weight have changed slightly and we have to make it. Adjustments. As you've seen from patients' reports, we have to make a concerted effort to look at comorbidities and other factors, not just cortisol. So if we're looking here, the Cushing's quality of life, we can see that it improved on treatment over several years.

How about levoketoconazole? This is a cortisol synthesis inhibitor approved by the FDA for the treatment of endogenous hypercortisolemia. It's administered twice a day orally and the approval was based on SONICS, which was a phase three open-label single-arm study, and LOGICS, a double-blind placebo control randomized withdrawal study, also phase three. So all these studies have been published.

However, at ENDO, additional post hoc analysis from SONICS looked at something that's very important for all of us in a clinic, can we determine in advance which patients will respond and which will not respond? So the answer is somewhere in between, but it's important data. There were 94 adults with

confirmed Cushing's and the dose in SONICS, it's exactly how we do in real life. Starting doses low, 150 twice a day, and then going up on the doses as tolerated and also based on how the patient is doing. And this particular post hoc analysis looked at the control... depending on how high the UFC was at the beginning. And you can see there were, you can see in red that patients that had less than 2.5 upper limits of normal had a much better response than the one that had more than five-time upper limits of normal.

Also what was important was that the liver-related adverse events were lower in patients that were ended up being controlled. So we don't know if this was due to the fact that because the cortisol was controlled and they had less liver-related disease, versus just the doses that were used were lower. As you can see there were different... No statistical significance was done specifically for that. So we can say that where you start is very important for the likelihood of achieving normalization and also for the rates of AEs, and this has not been shown before. So briefly so you can see a little bit better than numbers. The patients that for response rate were better responded if they were less than 2.5 or 2.5 to 3 versus more than five upper limits of normals. And the doses if you look, that's also important, that some patients needed higher doses to be controlled.

Look at the maintenance doses in red. The high UFC doses. But also all of the doses from maintenance had to be increased in order to achieve control. Also then though was a case series with three cases. And keep in mind this is a relatively new medication and there are no other studies besides the LOGICS and SONICS. So this was new a report from the MGH group. And I will go briefly through some of the cases. One was a 44-year-old male who previously took ketoconazole but stopped after surgery and several later Cushing's disease recurred with very high ULN and the patient refused surgery, underwent radiation and started levoketoconazole. You know that once you have radiation you need medications for many years most of the time. And patient achieved a relatively low dose of normal UFC, but had mild nausea and with a reduced dose did well.

A second case was pretty similar, just the patient had two surgeries this time and radiation and had a third recurrence. We see this all the time. The patient was treated with pasireotide, discontinued due to an abnormal liver test, and switched to keto, but the saliva cortisol remained elevated so then was switched again to levoketoconazole, low dose. Then for this patient with levoketoconazole, late-night salivary cortisol normalized Cushing's symptoms, improved brain fog, and mood disturbances.

And then the third case, this was a woman with presumed cyclic Cushing's disease. We all know that this is the most complex disorder to both diagnose and treat. This patient had transsphenoidal surgery with negative pathology, intolerant and uncontrolled with all other medications before, and tried four. Started levoketoconazole at the lower dose, and achieved normal saliva cortisol and UFC after one month. So success, however, the drug later was discontinued due to the development of a rash that was also observed with ketoconazole.

So you can see a range of case studies with what to look at how the UFC is normalized, how the saliva cortisol is normalized and also AEs at the same time. Another drug studied in extensor at ENDO was osilodrostat. Several new studies, in addition to LINC three and LINC four, were the initial large studies that the drug was approved. It's a cortisol synthesis inhibitor, mostly 11 beta-hydroxylase inhibitors, and also an aldosterone synthetase. It's approved, the same approval as the other drug, treatment of adults with Cushing's disease who cannot have surgery or who had surgery and have persistent disease. And it's oral medication also twice a day.

So links three and LINC four, this was a large study that we combined as a pooled analysis, of all the patients that have been on treatment. So we excluded of course placebo. I want to remind you that this was a little bit more complicated, and you'll see in the abstract and hopefully in the paper soon, that the exploratory analysis looked at the combination of all these patients which increases significantly in

number but then comes with some challenges. Particularly this presentation poster looked at blood pressure control and diabetes control.

You can see, and I will show you a little bit more details, that the patients taking anti-hypertension agents at the start of the study were 54%, decreased at week 72 and then the blood pressure improved. And I will show you soon the same thing for diabetes control patients taking medications, the numbers decreased over time. So keep in mind that that doesn't mean we don't have to look at the comorbidities in detail because in some patients with control of cortisol, you can decrease some of these meds, but not everybody's responding. So some patients will need even higher doses despite the control. So we have to look in significant detail. What's important here is the trend overall, as you can see in blue are patients who didn't take antihypertensive medications. In red, the one that took it.

And you can see over time of course the numbers are changing and of course, at 72 weeks are fewer patients. But you see the trend that it's decreasing with starting treatment and then persists in a relatively normal range, as you can see. However, we know now that the normal ranges are changing with the new guidelines. The same thing for diabetes. The curves are the same. Patients who are taking medications, and patients who are not taking medications. I'm showing you the A1c, but the glucose was also the same. You see improvement and then stay stable over time.

The other was very interesting... So these, LINC three and LINC four, as you know were large prospective international trials. Now the LINC six that attended the one-year interim report was presented as a real real-life study. So patients are treated with osilodrostat and then they are followed over time. But in real-world scenarios, different indications for disease. And as you can see this was again more focused on Cushing's disease than Cushing's syndrome. Were mostly female, and again makes sense because this is related to Cushing's disease. The median osilodrostat exposure was 5.5 months because the interim was at one year, but then again some patients got in late.

So if you can look at the three-month efficacy data, and I have it on the right and it's highlighted in red, was 71.4, pretty similar to the studies overall. And the late-night salivary cortisol, 50%. I wanted to point out that the median osilodrostat dose was five milligrams, which is lower than in the studies, with a minimum of one milligram per day. The approved lower dose is two milligrams, though I have many patients on one and the maximum 60 milligrams. And the 60 milligrams were for some ectopic patients.

That's one of the issues when the initial diagnosis is so different from Cushing's disease to adrenal to ectopic, the does not mean so much and the range is very important. For patients who discontinued treatment AE and 12 patients reported 44 AEs thought to be treatment related. The most common were vomiting and dizziness. Again, this separated new users from prior users. Because once you have an observational study, some of these patients were treated before. So if we're looking at the prior users in blue and new users in red, you can see that the normalization of UFC cortisol was higher in new users. The same thing with late-night salivary cortisol and serum cortisol.

Now how about these? I think from the clinical point of view, this graph from the poster is one of the most important ones. Of course, you can look in detail at all the numbers, but what I wanted to highlight is that you can have, as you can see, adverse events both in new users and also in prior users way more at the beginning when you start. So new users, as you can see for patients reported seven SAEs. So it's important to look at all patients all the time that are on any drugs, but especially with a potent drug with a risk of adrenal insufficiency that's higher than with others as is for osilodrostat, we need to follow very closely the patient.

And though it's decreasing over time, we can see with some intercurrent illnesses, we can see it later. So it's important, I always tell the patients, especially at the beginning, that could be withdrawal and then adrenal insufficiency. The likelihood of adverse events, of most adverse events, is decreasing over time.

However, you can still have it later. And I always give them steroids to have at home to take if needed and also injectable, and then call us.

How about Real 7? This was a retrospective non-interventional study evaluating the safety and effectiveness of osilodrostat. And this one... I told you the other one, it's so complicated because it has all the etiologies. This one had excluded Cushing's disease, so it's just any type of Cushing syndrome, non-pituitary, also in a real-world setting. And because Cushing's disease was taken out, as you can expect, the largest proportion of patients needing medical therapy was the ectopic Cushing's. That is more than half, which increases the severity of the disease.

So you already can see that because the median osilodrostat exposure and dose was 164 days. And again though it was five milligrams, you can see between one and 60, and many patients were on maximum dose. But 60 per day is the maximum approved dose. If we're looking at the results in efficacy for UFC, this was 44 at week 12 and 50% at week 24. And again, if you start very, very high at week 12, sometimes it takes time unless you start with block and replace and very high dose, it takes time to normalize again. The more you start higher doses to control, the more adrenal insufficiency, as you can see here, and sometimes even hypokalemia you can see.

28% died during the study. We expect this in patients with ectopic, which is caused mostly by cancers and adrenal cancers, 10% because of neoplastic progression and 14% is continued because of planned surgery for Cushing syndrome, either a tumor appeared or the surgery could be done. This was the largest study that looked at osilodrostat outside the Cushing's disease arena for all cases, and it gives us more perspective on how to use the drug.

Now, let's look at other studies. These were retrospective with off-label therapies for Cushing's syndrome. The study from NIH looked at ketoconazole, it's a cortisol synthesis inhibitor. It's approved in Europe to treat Cushing's syndrome but not approved by the FDA. There were 35 patients where the ketoconazole has been used with evaluation for efficacy. And as you can see, it's not UFC this time. For this particular study, the serum cortisol normalization was considered as controlled, and 17 out of 35 patients were controlled. What was important, and usually we don't do that, as you can... the median days between doses was two versus four for uncontrolled. So the increased doses were much faster than in other studies.

And you can see that if they were on a stable dose for three days after the increase, how the mean cortisol is decreasing. So this is important because that shows that efficacy and hepatotoxicity are linked, but also you can go up on the doses as needed. And yes, the LFTs rose to more than 30% in many, many patients, 27 out of 34. But the study says not everybody should stop the treatment. I have to say, usually, if it gets more than 30% I stop the treatment, sometimes even at less than twice per limit of normal. But based on this study, maybe we will change.

But I think the most important thing that you see in red is we can increase the dose much faster than we do for some patients, though I would be worried about adrenalin insufficiency in some of them. How about the etomidate? This is a cortisol synthesis inhibitor. It's the only intravenous one that we have available. We use it for patients in the ICU. This time was a case study of a woman with metastatic adrenocortical carcinoma, a poor surgical candidate, who required intubation. So again, none of the oral medications will work. And after eight days cortisol decreased from huge numbers to the goal on low-dose etomidate infusion. Another study showed, but not in intubated patients, that you can use it also on the floors though in the US this requires ICU.

How about prospective studies with investigational drugs? We're so lucky, and this year at Endo we had several studies presented. One with relacorilant, a selective glucocorticoid receptor modulator. It's highly selective with no activity at progesterone, mineralocorticoid or androgen receptors. It was the phase three double-blind randomized withdrawal study from GRACE which included patients with

Cushing syndrome and hypertension, hyperglycemia or both. Keep in mind that relacorilant because it's blocking the cortisol, the glucocorticoid receptor, the cortisol is a value. So we can check urinary-free cortisol, as you've seen in most of the other studies. So the endpoint has to be a clinical, the same thing as we did for mifepristone.

So for primary endpoint was considered loss of the hypertension control in patients that were on placebo, and of course safety. And for secondary hyperglycemia control as well as other cortisol-related comorbidities. So if you're looking here on the left, higher is hypertension. All patients with hypertension had a decrease in systolic and diastolic hyperglycemia. Also on the left, you see some decrease in area under the curve for glucose. And on the right, higher up you see blood pressure, hypertension responders who ended up randomizing and then also hyperglycemia.

Overall you can see the mean A1c decreasing from 7.2 with 0.3% in the diabetes range, from 7.6 decreased to 0.5, and the full-blown diabetes went from 8.1 with a decrease of 0.7. So depending on how high the patient was, saw more benefits with this drug for hyperglycemia. Significantly more patients were switched to placebo-loss hypertension. Keep in mind that this was the primary endpoint for this study. Furthermore, patients receiving relacorilant were 5.9 times more likely to maintain the hypertension response achieved during the open-label phase. Because that's what randomized withdrawal means. Patients are on a drug and then they switch on either a placebo or the drug. And then after that, they will go into extension in most of the studies.

What was interesting was that no clinically meaningful differences in adverse events were observed between the relacorilant and placebo arms. It's always nice from this point of view to compare the studies. Another drug atumelnant, it's a once-daily oral non-peptide, first-in-class competitive and selective melanocortin type 2 receptor antagonist that blocks ACTH-mediated G-protein activation and subsequent signaling. So this is a very interesting and novel concept. As you can see, it was a phase 1b/2a open-label study presented. Very small but very important data. Five patients with ACTH-dependent Cushing's, the study was done at NIH, received the drug. 80 milligrams every morning, 10 days, followed by four four-day washouts. By day two, so this is how the drug works, all participants experienced signs of adrenal insufficiency. The early morning cortisol was already low and started steroids. Many features of Cushing's syndrome improve.

So even in a short time blocking the ACTH-mediated G-protein activation is important. And of course, we need a much larger study, but for a signal, this was a very important data. Another drug that was presented was some data on an HSD-1 inhibitor, clofutriben, which is a novel mechanism of action to target the source of cortisol. It's an oral once-a-day administration. And complex monitoring might not be necessary based on the mechanism of action. Clofutriben has demonstrated the ability to lower intracellular cortisol levels in vital organs with a favorable safety and tolerability profile in five clinical trials.

I wanted to mention that all of them were outside the Cushing's syndrome arena, which showed improvement in glucose, A1c cholesterol and triglycerides. However, there are ongoing studies in Cushing's disease and adrenal Cushing's that we are awaiting to see if another drug with a different mechanism can potentially improve clinical signs and symptoms.

So in summary, I think this was a very important meeting for pituitary disorders, as I mentioned earlier, but particularly for Cushing's. An international quality of life survey demonstrated the ongoing burden of Cushing's, often starting more than seven years before an official diagnosis is made and continuing indefinitely. Pasireotide showed increasing full response rates over time in new users, stable rates in prior users and improvement in clinical signs of Cushing's at 36 months.

Also, another trial ad hoc analysis shows that a lower UFC at baseline predicted the likelihood of achieving normal UFC following six months of levoketoconazole therapy. And also even more important,

the lower UFC at baseline was associated with lower dose requirements and lower rates of potentially clinically important liver AEs. And that's very important from a clinical point of view. There were several studies on osilodrostat showing that it's generally well-tolerated and provides early and sustained cortisol control in patients with both Cushing's disease and other causes of Cushing's syndrome with improvements maintained or enhanced during long-term therapy. This aligns with previous clinical trial data that we have published.

Cortisol normalization, even more importantly, is associated with improvements in hypercortisolism-associated comorbidities in patients with Cushing's syndrome. And very important that doses in real-world settings vary by etiology and severity of the disease. So if I see a patient, I never tell them how high they would need to go on the doses. I usually say we're up-titrating very slowly. And as you can see the median dose was five milligrams per day overall, but some patients require much higher doses. And hypercortisolism-related events are the main AEs, especially at the start of treatment, but they show new also later, so patients have to be aware of all Cushing's drugs, especially the most potent ones.

Our retrospective review shows that raising ketoconazole doses very fast, q72 hours, is possible. I have never done it like this. Usually, I wait at least a week unless the patient is in the hospital. But this was done at NIH. Liver toxicity risk correlates with baseline AST levels. Also important from this study, is that while most patients experience a rise of more than 30%, the treatment should not be stopped unless the LFTs exceed three times the upper limit of normal. Etomidate is effective in controlling cortisol levels in patients requiring intubations, and we saw a case study. Relacorilant is a selective glucocorticoid receptor modulator that appears to be safe and effective in phase three studies. And Atumelnant, an oral MC2R antagonist, shows promise in early clinical studies.

And with that, I hope I showed you that these are very exciting times for the community of patients, caregivers and physicians dedicated to Cushing's syndrome. And I wanted to thank all of you for listening to us. Thank you.