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# Clinical Trial Updates in Cushing's Syndrome

**Announcer:**
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**Dr. Auchus:**
Hello, this is CME on ReachMD, and I'm Dr. Richard Auchus. Today, I'll be discussing the treatment landscape of Cushing's syndrome and some recent trial data, and I'll be focusing today on Cushing's disease.

If surgery fails, if people have recurrent disease, there are several classes of drugs. I'll start with pituitary-directed therapy with pasireotide. This is either given subcutaneously twice a day or as a monthly intramuscular injection as an LAR form. This binds to the somatostatin receptors, in particular, not just the type 2 but also the type 5 receptors, which are typically found on corticotrope adenomas.

Now in the initial study with the subcutaneous form, urinary free cortisol control was found in about a quarter of the patients but reduction in about 90%. Subsequent studies that looked at people with mild disease showed 40% to 60% control rates and some tumor shrinkage during long-term therapy. So particularly useful in people for whom you're worried about tumor growth. However, the main adverse event is that because of the somatostatin type 5 receptor on the beta cells, that they can get hyperglycemia, worsening of hyperglycemia, or new-onset diabetes as a result.

The next group would be the steroidogenesis inhibitors, and those would be osilodrostat and levoketoconazole.

So osilodrostat, which has been studied in the LINC 2, LINC 3, and LINC 4 trials, is an 11-hydroxylase inhibitor that inhibits the last step in cortisol biosynthesis.

So it's a very potent drug, usually start 2 mg twice a day, sometimes even lower. And what has been seen in the trials is a 60% to 80% control of urinary free cortisol. And then in long-term extension studies, patients seem to stay in control. They don't escape from this drug. In fact, sometimes they have to have their dose reduced during long-term therapy. And now I would say that the concerns with this drug is because of the positioning of where the target is in the steroidogenesis pathway, there can be accumulation of mineralocorticoids and androgens because of the precursors that build up above the block. Hypertension and hypokalemia worsened in about 7% of people in the clinical trials, whereas androgen excess did not really seem to be a problem, as testosterone tends to decline after a possible initial rise in the women taking this drug. But those are 2 things that need to be monitored.

Levoketoconazole inhibits multiple enzymes, primarily the 17-hydroxylase enzyme. And it is the relevant enantiomer, it is the 2S,4R enantiomer of ketoconazole, which is more potent in inhibiting all the steroidogenic enzymes. And in particular, the effect on 17-hydroxylase is going to androgen, so in women who are bothered by androgen excess, this is a potential benefit. In men, this can be a detriment, particularly when higher doses are needed. The SONICS and LOGICS studies showed about a 30% to 60% disease control rate and then improvements in comorbidities of the disease over time.

Lastly, there is mifepristone, which is a cortisol receptor blocker, a glucocorticoid receptor inhibitor. Probably the most impressive results from the SEISMIC trial was the improvements in glycemia. So this drug is actually approved for use in Cushing's syndrome of any sort with associated hyperglycemia. And the improvements in glucose control were quite rapid and quite marked, although the people in this study had very severe Cushing's, so they were starting from a very high point of comorbidities. And there hasn't been a lot of new data since that initial publication about 10 years ago.

Any treatment is better than no treatment, and any dose is better than no dose, but first do no harm and be patient. Cushing's is a chronic disease and people need to be able to tolerate this in the long term.

Thank you for your attention.

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