Maria Fleseriu:

Hello everybody. It's my pleasure to talk to you today about updates in medical management of Cushing's syndrome and will focus on the recent consensus with the society guidelines. I'm Maria Fleseriu from Oregon Health and Science University in Portland, Oregon. And it's my pleasure to have with me for discussion my co-chair from the Pituitary Society Consensus Guidelines, A friend at the colleague, Professor Beverly Biller from Harvard Medical School and Massachusetts General Hospital. Thank you Beverly.

Beverly Biller:

Great to see you and it's always fun to talk about the guidelines.

Maria Fleseriu:

And these are my disclosures for the last two years. I was PI, and with Research Funding to OHSU. And from HRA Pharma, Recordati, Xeris and Sparrow, occasional scientific consulting fee. When we're talking about treatment of Cushing's, what are the goals? And sometimes they are moving target and not easy to do all of that. Normalization of biochemical changes with minimal morbidity, easier said than done. Reversal of clinical features with quality of life improvement. And then long term control without recurrence that as you heard earlier, it's not as good as we used to think, many patients will recur. This is a complex algorithm and I'm going to show you more details, but just to see that for patients with Cushing's, we have to focus first on what's the main treatment and if they have Cushing's disease, rarely they need preoperative medical therapy, especially in US it's not used very frequently, we discuss at the guidelines that in other countries it's used more but the pituitary surgery remains first line of treatment.

However, many patients will not be in remission. The numbers for microadenoma go to 80 - 90%, but for macroadenoma it's even less. Overall, what we have recommended and suggested, and this is not new, but it's sometimes not done, patients with Cushing's disease need to have surgery in a Pituitary Center of Excellence, done by an experienced surgeon and then followed by a multidisciplinary team. And what we have also recommended that we don't have enough is the outcomes of pituitary surgery, in addition to the cost effectiveness should be reported for all these centers. Now what happens if the patient is not in remission? If they have persistent disease, then we have to go back and I'm not going to talk too much in detail today, is we have to go back to the drawing board and decide if the patient has Cushing's.

If the histology is negative, then we step back and think what's going on. But then if the patient has persistent disease that's confirmed, then main treatment would be medical therapy and sometimes we also use other treatments as radiation for example, and then we follow the patients. However, re-operation, especially for patients with histology positive, it's also an option. The repeat surgery is potentially curative but doesn't work in all the cases, it's clearly lower in about 50% and with addition of hypopituitarism also in about half of the patient so I tell the patient that yes, you have a chance of remission and then patient preference is very, very important for that. Looking at what's next, repeat surgery or medical therapy? We have now several drugs available and you see here on the list based on where they work, not all of them are FDA approved and I will mention which one are on label and which one are off label.

We have neuromodulators of ACTH release that we will talk about later. We have adrenal steroidogenesis inhibitors and we have a glucocorticoid receptor blocker. Each of them work in different ways and sometimes we use combination. Let's focus from the adrenal steroidogenesis inhibitors that are now the mainstay of therapy. We had two recently approved, Levoketoconazole is the one that's the most recent approved. It's an orally administered ketoconazole stereoisomer and it's a very potent

steroidogenesis inhibitor. Now keep in mind that ketoconazole is racemic mixture of two enantiomers and it's an azole antifungal drug approved for treatment of endogenous Cushing's in Europe and used of label in the United States. Now the main study that we had with levoketoconazole, was the SONICS study. It was a phase three, multicenter, open-label, non-randomized, single-arm study. If you're hearing me detailing all these type of studies, this is very important because how we look at the result.

And also it's important because sometimes we can compare the direct numbers because the studies are so different. This study for example, looked at the mean 24-hour urinary free cortisol of at least 1.5 times upper limit of normal. And the primary outcome was also different compared with other studies. The was proportion of patients with normalization at the end of maintenance without those increase during that maintenance. In this study, 31% were responders and if you have look at the mUFC normalization overall, patients had very urinary high cortisol and then significantly decreased by one month and then hover around the normal and 31% responded overall. If we look at clinical features in that study published later, not as in the main paper, acne, hirsutism and peripheral edema improved. And if we're looking for clinical signs and symptoms, and you've seen even a diagnosis, sometimes some patients have more features than others and it's not always correlated with how high the urine need.

Furthermore, with treatment as you can see in green is now changed, orange is worsening, some of the patients in blue here will improve overall, but some patients wouldn't change. And this is really related with where they started on baseline. If we look at the quality of life questionnaire, patients improved overall in the study with this drug. Moving on, another study, LOGICS, this time was a phase three, double-blind, placebo-controlled, randomized withdrawal study. Also the UFC was at least 1.5 times upper limit of normal. And keep in mind that if this higher they start patients, the rates of control could be changed when we look at that. The primary outcome in this study that had a placebo was proportion of patients with loss of UFC response during randomized withdrawal phase.

If we're looking briefly what happened with the patients, there were 84 patients enrolled, few of them came from the previous study I shown you, they were treated with levoketoconazole and then 44 patients that were normal randomized in an intent to treat, some of them treated with levoketoconazole, some with placebo, and then patients after that entered and completed the restoration phase, levoketoconazole.

Let's look at the results. Keep in mind the primary endpoint was loss of therapeutic response so you can see here this was the loss of therapeutic response with levoketoconazole and look at with placebo. And then if we look at normalization, that was a secondary endpoint for thinking the first study, UFC was primary endpoint was 50% with levoketoconazole versus 4.5 with placebo.

Looking at the adverse events, and I'm going to show you for all the studies is, there are AEs in general, that some of them are drug related as you can see here in 40% of cases, few of them are serious. What's important to look for all the studies are the most common AEs and also in my view, I look at the ones that possibly are related to adrenal insufficiency and nausea. Sometimes could be withdrawal, could be adrenal insufficiency was seen in a lot of patients same with hypertension and headaches.

For levoketoconazole, the study had specific AEs of special interest and liver related in these studies were almost 11%, QT prolongation almost 11%, in adrenaline sufficiency almost 10%. In general, based on the studies and on clinical practice, though the drug is recently approved, we need to obtain baseline liver test and EKG and correct hypokalemia and hypomagnesemia before starting the drug. I usually start the recommended dose twice a day and then slowly, slowly titrating and you'll see that this is basically for all the drug titrate based on cortisol changes when you can measure individual vulnerability improvement in signs and symptoms and also where we start going to maximum dose 60 milligram, twice a day and a drug has Drug-drug interactions that we have to look for.

Now levoketoconazole has an FDA warning for LFT elevation and QTc prolongation so we need to perform EKG in all patients as I mentioned earlier, but also to use with caution if risk factors for QT prolongation. And keep in mind that patients with Cushing's are more prone to increase QT so this is very important to look at in detail, monitor closely for adrenal insufficiency and usually if it's either withdrawal or adrenal insufficiency, I decrease the dose and sometimes even stop as needed.

Let's switch gears and talk about another adrenal steroidogenesis inhibitors. This time it's an oral inhibitor of 11 beta hydroxylase, but also it is inhibiting aldosterone synthesis. There were several studies over the years, I'm not going to show you all of them that shown results with this drug. The phase three, LINC 3 was a prospective, multicenter, open-label with a double-blind randomized withdrawal period.

So it had four steps and again, this is very important when we look at numbers and even attempt to try to compare, but the primary objective for the study was to compare response at the end of period 3 so the randomization versus placebo and the complete response with drug versus placebo at week 34 was 86% for the drug and 10% versus placebo. And at week 24 overall, 72 out of 137 patients maintained the complete response without up-titration. You'll see that the numbers defer even for the same drug from study to study. This study had some patients that also had radiation and if you look here on the left, the differences were not very high if it was history of radiation between osilodrostat and placebo and also based on doses which is less than five and more than five, the radiation did not play a huge role.

How about adverse event? This is osilodrostat versus placebo. And you can see for looking at all the AEs, were 72 for the drug, also very high with placebo 66. Keep in mind these were patients with Cushing, so we expect to have adverse events. However, we really need to look at the details. These were adverse events requiring those adjustment that was 19% for the drug, 14% versus placebo, and then the most common study emergent adverse events, were several that we need to notice, nausea, anemia, arthralgia, headache, asthenia. We really have to look into this, again adrenal insufficiency versus withdrawal overall.

The next study and the most recent one published this year, was a phase three, multicenter trial. This time the placebo was at the beginning, so it was 12 week randomized, double-blind, placebo-controlled, osilodrostat to placebo, 2:1 and then everybody got on treatment open-label.

I wanted to point out that the UFCs were lower at baseline, it was 1.3 and the primary endpoint was proportion of randomized patients with normal UFC at week 12. And if we're looking now overall this is percentage of patients that are controlled from week one, week two, week five, week eight, week 12. Clearly increased significantly and almost reach 80% at week 12. How about these? The placebo-controlled period and overall period have different types of AEs. I wanted you to focus just the overall period. All patients, almost half of them, had decreased appetite, arthralgia, several of them had fatigue, nausea, headache, myalgias were getting to 26%. And then adrenal insufficiency per se, 24%. Doesn't mean that this was just the rate of adrenal insufficiency for this drug because all of these symptoms potentially could have been adrenal sufficiency and not just withdrawal but for all the studies when we look at the AEs is how they are reported by the primary investigators.In clinical practice, we should really look at this and watch for and ask the patients.

The most recent study that we have contributed to both me and Dr. Biller, was the LINC 3 study extension. This has been recently published and this is the data I've shown you earlier, this is the mini UFC with average osilodrostat dose for the main study and then the patients continued in extension and as you can see the UFC remain normal for large proportion of patients and they were not on a very high dose overall hovering around five six and improvements in cardiovascular, metabolic related parameters, physical manifestation and cure, quality of life also improved so we have now long term data showing that patients could be, it's true, over time the numbers are decreasing, could be longer

term controlled on adrenal steroidogenesis inhibitors. For osilodrostat, it's important also to correct the hypokalemia and hypomagnesemia and obtain baseline EKG prior to starting to initiate the recommended one.

It's two milligram orally BID, with titrating very, very slow and no more frequently than two weeks based on the same things you heard earlier. Maximum recommended dosage is 30 milligram twice daily and drug-drug interaction. Closely monitoring for adrenal insufficiency, this is a potent drug. Dosage reduction or interruption may be necessary and again we have to watch for QTC prolongation and also elevation because the mechanism is different in Adrenal Hormone Precursor, androgen monitor for hypokalemia, worsening of hypertension was rare overall, but in some patients, edema and hirsutism.

There are, as I mentioned earlier, several other adrenal steroidogenesis inhibitors that are off-label in US.We have used them for many, many years. Ketoconazole is one of them also Metyrapone that was on and off available. Mitotane, that's mostly beneficial in adrenal cancer, rarely using US otherwise. And Etomidate that's the only intravenous adrenal steroidogenesis inhibitor or medication for Cushing's available for that matter. Has a very rapid action and for few patients a year, we have to use it with intensive ICU monitoring but it decreases the cortisol very well.

Now that we have discussed about all the adrenal steroidogenesis inhibitors, I have a question for you Beverly. In real life, how do you use the most recent approved adrenal steroidogenesis inhibitors, osilodrostat and levoketoconazole, which is that dose you use and how you titrate?

Beverly Biller:

Yeah, that's a great question and I'll just start by saying how wonderful it is that we now have several new medicines from which to choose, which is obviously very beneficial for our patients because we can individualize the therapy. Levoketoconazole is the one that's most recently approved and so we're just starting to use it, but therefore we are using the prescribed dose which is 150 milligrams twice daily. The osilodrostat has been around a little bit longer because it was approved a bit earlier and there the approved starting dose is two milligrams twice daily. I must say that I often give a lower dose than that of one milligram twice a day because unless we're in a rush with a patient who has severe Cushing's, we find that patients tolerate the gradual up titration better and perhaps there will be a lower rate of adrenal insufficiency. `

Maria Fleseriu:

Thank you Beverly. And talking about the severe hypercortisolism, when do you use block and replace? Can you describe for the clinicians that are watching us?

Beverly Biller:

Yeah, I'll just mention first that as you know at the consensus meeting, that was a topic that was quite controversial because there are people who never use block and replace, there are people who pretty much always use block and replace and then probably most of us fall somewhere in the middle. I'm towards the end of not using it too often, mainly because when we replace after blocking cortisol production, I think we overdo it sometimes and so we ourselves are creating Iatrogenic cushing's, but it can be very valuable when someone is seriously ill and perhaps developing sepsis and hospitalized, you really want rapid control of the cortisol so you can give high doses of adrenal blocking drugs and then give back some glucocorticoids. That's when I tend to think about using it.

Maria Fleseriu:

Great, thank you.

Let's switch gears now and talk about drugs for Cushing's disease. These are not for all patients with Cushing syndrome. The work at the pituitary level. We have pasireotide that is a somatostatin receptor ligand, FDA approved works rapidly control rate is approximately 50% in mild Cushing's disease. And when I'm thinking to use it otherwise, the main studies that I'm not going to show you today showed response rate at about 20% for all comers improves clinical signs and symptoms induces to more shrinkage and also for rare patients that have pituitary macroadenoma. This is the drug that I'm thinking first. Considerations, side effects, GI disturbances, nausea, cholelithiasis all the somatostatin receptor ligand. However, in addition to others, hyperglycemia is very frequent 60 to 70% of patients in all the studies and in my clinical practice so we really have to watch for blood glucose level.

What was interesting for this study and looking forward to see even more data, whereas the clinical improvements were significantly higher for patients that had normal urine and normal mLNSC cortisol, you don't have even have to look at all the details of this particular slide, look just the blue, controlled or very few patients, but these patients were the one that had better systolic blood pressure, better diastolic blood pressure and better weight. Maybe the studies had urinary free cortisol endpoint, so it's hard to look in more details than here, but maybe we need to look at other markers of what we define as biochemical control. Also, cabergoline could be used for Cushing's disease, not for other patients with Cushing syndrome. The meta-analysis that you know it's as good as the studies that could be included was about 30% of patients. However, this is not a drug that works for everybody.

We know now that there are more impulse control disorders, higher rates than we used to think from hypersexuality with pathological gambling and we have to use higher doses to actually control the Cushing's. I use it mostly for combinations, but I rarely, rarely use it for patients with Cushing's disease as monotherapy. Now the third mechanism of action is blocking the glucocorticoid receptor blocker. Again, we go back for all patients with Cushing syndromes and we are not just at the Cushing's disease, the drug is approved to treat hyperglycemia and adults with endogenous Cushing syndrome based on the phase three trial called seismic, where we had 50 patients in doses between 300 and 1200, the large majority were on 900, improved significantly in the glucose even with decreasing in insulin and clinical signs and symptoms. Considerations, adrenal insufficiency, moderate to severe hypokalemia, we can measure cortisol because this is blocking the glucocorticoid receptor.

We need to base all the decision on clinical parameters and also the thyroid function needs close monitoring. As a brief summary of all the medical therapies that I have shown you, if you're thinking, "Oh, there are so many now that are approved, when should we use one versus the other?" That really depends and we have discussed in the guidelines and also clearly a lot in the discussion in the consensus meeting, that really depends also on countries, on availability and on cost of the drugs. But in general, if we want rapid normalization, adrenal steroidogenesis inhibitor is recommended, Oral osilodrostat or metryapone versus intravenous etomidate for rapid normalization. I wanted to point out at the time of the consensus meeting, levoketoconazole was not approved. For Cushing's disease, as I mentioned earlier, if it's residual tumor present, pasireotide or cabergoline so drugs that work between three level are preferred first if they work, if not, we have to control the cortisol.

If the patient has history of bipolar or impulse control disorder, I will definitely consider avoiding cabergoline. And then Ketoconazole, levoketoconazole might be favor for ease of dose titration; concerns about inducing hepatotoxicity and the need for monitor liver enzymes can lead to underdosing so we really have to look at efficacy based on the patient being up titrated properly. If the patient is pregnant or potential for pregnancy was a lot of discussion, of course nothing is approved, none of them can be used. But there are some cases on cabergoline or metryapone published. And then drug intolerance or side effects and concomitant comorbidities present should also guide the medication choice and we have spent a lot of time, and really this goes to it has to be individualized treatment. Combination therapies, I'm not going to go in a lot of details are just for you to know that they exist.

Which one we should start first? What dose? There were very few studies looking at this in this day in detail and very few prospective and several of them just presented, not even published. But definitely this is something that we should look in more detail because it's possible we lower doses of two medications. If there are no Adverse Events, we're able to control more patients.

I have reviewed for you now several of the medication when to use it and what we have discussed in the guidelines about factors to consider one versus the other, but we didn't talk about other treatments besides the repeat surgery and the medication. When do you use other treatments and where do they fit in the treatment algorithm?

Beverly Biller:

Yeah, so before we had all of these wonderful medicines from which we can choose, of course we only had the options of repeat the pituitary surgery, the oldest treatment, removing both adrenals or giving radiation while also treating with medicine. And so if we think about those, the repeat Transsphenoidal surgery can be a good solution if done by an expert pituitary surgeon, although the remission rates are lower than initially and the risk of hypopituitarism is higher than at the first operation, nevertheless that can be a good choice for some patients. When we think about bilateral adrenalectomy, that is the treatment that was used in the 50s and 60s and it has the advantage of immediately providing remission because there's no production of cortisol if the adrenals are gone and it's usually permanent, it's well tolerated. If it's done laparoscopically, it has more risks because potentially it's abdominal surgery, sometimes it needs to be converted to open if there are complications.

Those patients need both lifelong mineralcorticoids and glucocorticoids and that can have some issues as well. But what we really worry about in those patients is the long term risk of the tumor that's not been treated in pituitary Cushing's progressing formerly called Nelson's syndrome, now we tend to call it [inaudible 00:28:08] tumor progression. And so those are things we worry about. But as we discussed at the consensus meeting, this really now is considered a last resort in most patients. The exception being that some people feel it's a good choice in women who may want to achieve fertility. And it also is a good choice if someone can't be controlled even with combinations of medications although I think that's less likely nowadays. Just to finish up, I'll mention radiation.

Radiation delivered to the pituitary blend is also well tolerated, especially if we use stereotactic radiosurgery and affords tumor control in most patients, it doesn't do quite as well in terms of cortisol control and of course when we give radiation, we have to be giving medication at the same time because radiation has the disadvantage of taking years to work, sometimes a year or two, sometimes much longer than that. And has the risk of developing pituitary deficiencies, potentially damaging nearby structures and secondary neoplasia with about a 1% rate of that at 10 years and a 2% rate a 20 years so these patients need long term scans to monitor for that. We also need periodically to withdraw the medication we're giving to see whether the radiation has taken effect. The guidelines meeting that we participated in really saw this as something to use if there's a persistent tumor in an unresectable area in patients who couldn't be easily controlled or an aggressive tumor. Is that when you would use it?

Maria Fleseriu:

I agree. I think there are differences between countries and also the guidelines that we heard several from experts, from many other continents, not just from US. And I think it's very variable. I use it rarely unless it's a tumor that's growing extremely rare. But pituitary macroadenomas in Cushing's could be very aggressive or if none of the medical therapies are working or the patient doesn't tolerate, but much, much more rare than other countries that don't have any of the medications and then even 10 years later for a chance of 50%, they will take it rather than not treat overall. And I completely agree.

Thank you so much for this overview of all the other treatments and hope you liked our discussion and you liked the really intense overview of medications and we are both, as you heard, very happy that from nothing FDA approved 10 years ago now we have four medications that we can offer to our patients that are improving their symptoms are improving their biochemical control.

And we have data for long term use right now so I think we're not where we want to be to have perfectly individualized treatment, but we're really striving for excellence for care for patients with Cushing's.

In conclusion, I've shown you this complicated treatment summary that we have reviewed almost line by line. And I really want to thank you for the attention and to highlight that the patients with Cushing syndrome and also with Cushing's disease need individualized treatment and we have to make significant efforts to diagnose the patients earlier. Maybe if the disease is less serious, the outcomes will be better also. Thank you.