Korlym (mifepristone) in Cushing's syndrome: why cortisol cannot guide treatment

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Mifepristone is the only glucocorticoid receptor antagonist approved in Cushing's syndrome, and it behaves unlike every other drug used in the condition. It does not lower cortisol. It prevents cortisol acting. Cortisol and ACTH therefore rise during successful treatment, there is no biochemical marker of response, and the characteristic adverse effects follow directly from the mechanism rather than arriving as surprises.
This page answers the questions clinicians and patients ask about it, each under its own heading, and is explicit about the limits of the trial evidence.

KEY TAKEAWAYS

- Mifepristone blocks the glucocorticoid receptor. It does not reduce cortisol production, which separates it from every steroidogenesis inhibitor used in this disease.
- ACTH and cortisol RISE on treatment through loss of negative feedback. That is expected pharmacology, not treatment failure, and neither can be used to titrate the drug.
- Titration is clinical: glycaemia, blood pressure, weight and the features of cortisol excess. There is no laboratory test of response.
- Hypokalaemia and oedema follow from unopposed mineralocorticoid activity and are anticipated, monitored and treated, often with a mineralocorticoid receptor antagonist.
- Adrenal insufficiency must be recognised clinically, because cortisol concentrations are high and uninformative.
- Mifepristone is a potent abortifacient and is contraindicated in pregnancy.
- SEISMIC, the pivotal trial, was open-label, had no placebo control and ran 24 weeks in a disease treated for years. Relacorilant has now reported a randomised phase 3, but the two have never been compared head to head.

What is Korlym approved for, and what does that indication actually say?

Korlym is mifepristone at the doses used in endocrinology rather than in reproductive medicine, and its approved use is narrower than it is usually described.

The indication is the control of hyperglycaemia secondary to hypercortisolism in adults with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance, and who have failed surgery or are not candidates for it. Three qualifications in that sentence do real work and are routinely dropped when the drug is summarised.

It is for endogenous Cushing's syndrome. Exogenous steroid excess is treated by reducing the steroid, and a glucocorticoid receptor antagonist has no place in it. It is indicated for the control of hyperglycaemia, not as a general treatment for Cushing's syndrome, which matters because the trial was built around that endpoint and the evidence follows the indication rather than the other way round. And it sits after surgery in the sequence, because transsphenoidal surgery remains first-line for Cushing's disease in the Endocrine Society clinical practice guideline.

The distinction between Cushing's disease and Cushing's syndrome is worth holding separately here, because it changes the monitoring. Cushing's disease is the subset caused by an ACTH-secreting pituitary corticotroph tumour. Cushing's syndrome is the broader category including adrenal and ectopic sources. Mifepristone is indicated across the syndrome, but the pituitary subgroup carries a specific surveillance requirement that the others do not, for reasons that follow from the mechanism.

One further point of confusion is worth closing. The same molecule at much lower doses is used in reproductive medicine, and the association is strong enough that pharmacy systems, patients and occasionally colleagues react to the name rather than the indication. The endocrine dose is several times higher and the purpose is unrelated, but the antiprogestational activity does not disappear at the higher dose, which is why the contraindication in pregnancy is absolute rather than theoretical.

How does it work, and why does that change everything about monitoring?

Mifepristone is a competitive antagonist at the glucocorticoid receptor. It does not reduce cortisol production. It prevents cortisol acting once produced.

That is a fundamentally different mechanism from every other drug class used in this disease. Steroidogenesis inhibitors, including ketoconazole, metyrapone, osilodrostat and levoketoconazole, lower circulating cortisol by blocking its synthesis. Pituitary-directed agents act on the corticotroph tumour to reduce ACTH drive. Both of those lower the hormone, which means the hormone can be measured to see whether they are working. Mifepristone leaves the hormone where it is, or rather sends it higher, and blocks the receptor instead.

Almost everything difficult about using this drug follows from that single fact. It explains why the laboratory cannot guide treatment, why the adverse effects are what they are, why adrenal insufficiency is hard to detect, and why a clinician new to the drug can look at a set of results and conclude the opposite of the truth.

It also explains why the drug is titrated slowly and clinically. With no biochemical endpoint to aim at, dose escalation proceeds against clinical response and tolerability, and a published analysis has examined the relationship between mifepristone dose, efficacy and tolerability specifically because that is the practical question a prescriber faces with no number to anchor to.

There is one more consequence worth stating in advance. Because the drug competes with cortisol at the receptor, its

effect can be overcome by giving enough exogenous glucocorticoid. That is inconvenient in theory and essential in practice: it is what makes over-blockade treatable. A patient who becomes adrenally insufficient on mifepristone is not left waiting for the drug to clear, but it does mean the glucocorticoid doses needed are higher than those used for ordinary replacement.

Why do ACTH and cortisol rise, and how is response judged instead?

This is the question most worth getting right, and the one that most often catches out clinicians meeting the drug for the first time.

Because mifepristone blocks the glucocorticoid receptor rather than lowering cortisol, it interrupts negative feedback at the pituitary. The pituitary reads the periphery as under-exposed to cortisol and increases ACTH output. Cortisol rises with it. A rising cortisol on mifepristone is the expected pharmacology of a receptor antagonist working as designed, and it is not evidence of treatment failure.

The practical consequence is absolute: cortisol and ACTH cannot be used to titrate this drug or to judge response. There is no biochemical marker of efficacy. Titration is clinical, against glycaemic control, blood pressure, weight, and the clinical features of cortisol excess. A clinician who orders a cortisol at six weeks to check progress will get a number that is higher than baseline and means nothing about whether the patient is better.

In Cushing's disease specifically the rise has a further implication. A study of long-term treatment examined changes in plasma ACTH and corticotroph tumour size in this population, and the possibility of tumour progression under sustained loss of feedback is why patients with pituitary-driven disease need imaging surveillance rather than biochemical monitoring alone. That is a real and specific obligation attached to prescribing, and it does not apply in the same way to adrenal or ectopic disease.

What replaces the laboratory is a structured clinical review. Glucose and glycated haemoglobin for the approved endpoint, blood pressure, weight, the cushingoid features, and a direct enquiry about the symptoms of cortisol withdrawal. That is more work than reading a cortisol, which is precisely why the temptation to read a cortisol persists.

What did SEISMIC show, and what are its limits?

The trial the approval rests on is SEISMIC, a 24 week multicentre study in endogenous Cushing's syndrome. In the diabetes cohort it demonstrated improvement in glucose control, and clinical improvement was also reported in the cohort enrolled on the basis of hypertension.

Two features of the trial should shape how every result from it is read, and both are usually omitted. It was open-label with no placebo control. For an objective endpoint such as glucose that limitation is modest. For a clinical global assessment, where an unblinded investigator scores an unblinded patient, it is substantial, and the global assessment results should carry considerably less weight than the metabolic ones.

The second is duration. SEISMIC ran 24 weeks in a disease that is treated for years, sometimes indefinitely where surgery has failed and radiotherapy has not yet taken effect. Everything known from the randomised setting about this drug concerns its first six months.

Longer-term data exists and is observational. A follow-up analysis of SEISMIC together with its long-term extension examined sustained effects beyond the original trial period, and an analysis of dose against efficacy and tolerability drew on the same population. Neither has a control group. That is a reasonable evidence base for a rare disease where a long placebo-controlled trial would be difficult to justify, and it is not the same thing as demonstrated long-term efficacy.

The rarity of the disease also shapes what can fairly be asked of the evidence. Endogenous Cushing's syndrome is uncommon, the surgically refractory subgroup smaller again, and the subgroup of those with diabetes smaller still. A trial powered to modern standards in that population would take years to recruit. Holding this drug to the evidentiary standard of a cardiovascular outcomes trial is not a fair test, and neither is treating an open-label result as though it were a blinded one.

What happens to weight and to diabetes?

Glycaemic improvement is the approved indication rather than a secondary benefit, and it is the endpoint the registration trial was built around. Glucocorticoid receptor blockade improves insulin sensitivity, and in the diabetes cohort of SEISMIC glucose control improved over 24 weeks.

The clinically urgent consequence runs in the other direction. As cortisol action is blocked, insulin resistance falls, and anti-diabetic medication that was appropriate at baseline becomes excessive. Patients on insulin or sulfonylureas are at real risk of hypoglycaemia, and the risk arrives as the drug starts working rather than as a late complication. Doses need reviewing at initiation and at every escalation, and this is a foreseeable event to be planned for rather than an adverse reaction to be discovered.

Weight reduction is among the better-documented effects. A follow-up analysis of SEISMIC and its long-term extension examined sustained weight loss specifically and found reduction maintained beyond the original trial period.

Two cautions belong with that finding and are frequently stripped away when it travels. The weight loss is a consequence of reversing pathological cortisol-driven weight gain in a population that has it, and says nothing whatever about mifepristone in people without Cushing's syndrome. And the long-term extension was not placebo-controlled, so the durability observed is uncontrolled observation rather than demonstrated maintenance of effect.

For the consultation itself, both effects are worth raising early and for opposite reasons. Weight loss is the change patients most want and most notice, and setting it out as a consequence of reversing cortisol excess rather than as a weight-loss drug keeps the expectation accurate. Glycaemic improvement is the change that carries the immediate risk, and a patient who understands why their insulin is being reduced is far less likely to continue the previous dose because it is what they have always taken.

What are the side effects, and why are they predictable?

The adverse effect profile follows directly from the mechanism, which makes it unusually foreseeable. Almost nothing here should come as a surprise to a prescriber who has understood what receptor blockade does.

Hypokalaemia is the most important and is treated separately below. Endometrial thickening and vaginal bleeding occur in women through antiprogestational activity at the doses used, which is a consequence of the same molecule's other receptor affinity rather than of glucocorticoid blockade. Fatigue, nausea, headache, arthralgia and oedema are common. Consensus recommendations on the clinical management of patients treated with mifepristone have been published and address monitoring and management of these in practice.

Adrenal insufficiency deserves particular attention because the usual safety net is absent. Excessive receptor blockade produces the clinical picture of cortisol deficiency while circulating cortisol concentrations are high and rising. A clinician who checks a cortisol in a patient who looks unwell will be reassured by a number that is entirely uninformative. Recognition is clinical: nausea, vomiting, fatigue, hypotension, and a patient who has deteriorated since the last dose increase. Treatment is to hold the drug and give glucocorticoid at doses high enough to compete with the antagonist.

Mifepristone is a potent abortifacient and is contraindicated in pregnancy. This is not a footnote and does not belong at the end of a list. Pregnancy must be excluded before treatment and prevented during it, and the antiprogestational activity that makes the drug an abortifacient is the same activity producing the endometrial effects above.

The endometrial effects have a practical follow-on that is easy to miss. Vaginal bleeding in a woman on mifepristone has an obvious pharmacological explanation, and that obviousness is the risk: it invites attribution without assessment, in a population whose cortisol excess and age distribution already warrant a low threshold for investigating abnormal bleeding. The drug explains the finding, and explaining a finding is not the same as excluding the alternatives.

Why do hypokalaemia and oedema happen, and how are they managed?

Both follow from one mechanism, and understanding it makes the management obvious rather than something to be memorised.

Cortisol can activate the mineralocorticoid receptor. In health it is prevented from doing so by 11-beta-hydroxysteroid dehydrogenase type 2, which converts cortisol to inactive cortisone at mineralocorticoid target tissue. In cortisol excess that enzymatic protection is overwhelmed by substrate. Mifepristone then blocks the glucocorticoid receptor, raises cortisol further, and leaves the mineralocorticoid receptor entirely unblocked. The result is mineralocorticoid excess: potassium loss, sodium and water retention, and hypertension.

Management follows the mechanism directly. Potassium is measured before starting, repeatedly during titration, and after every dose increase, because the effect scales with the degree of blockade. It is replaced when low. Where replacement alone is insufficient, a mineralocorticoid receptor antagonist such as spironolactone blocks the receptor that is actually being over-stimulated, which addresses the potassium and the fluid retention together rather than treating them as two problems. The published consensus recommendations set out this approach.

Hypokalaemia here can be severe and is not a nuisance effect. It is the adverse event most likely to require intervention, it is predictable from the first prescription, and it is the reason this drug should not be started by a clinician who is not going to see the patient again within weeks.

Oedema is the same physiology presenting differently and is managed alongside. A patient reporting swelling and a patient with a potassium of 3.0 are showing two faces of one process, and treating them as unrelated leads to a diuretic being added where a mineralocorticoid receptor antagonist was the answer.

How does relacorilant compare?

This is now answerable from randomised evidence rather than from mechanism and hope, which was not true until recently.

Relacorilant is a selective glucocorticoid receptor modulator. The distinction from mifepristone is that it lacks the

antiprogesterone activity responsible for the endometrial effects, and is intended to avoid the mineralocorticoid consequences that produce hypokalaemia. On mechanism alone it addresses the two adverse effects that most constrain mifepristone use.

GRACE, a multicentre phase 3 double-blind placebo-controlled randomised-withdrawal study, has now reported efficacy and safety in Cushing's syndrome. That is a considerably more rigorous design than SEISMIC: randomised, blinded, and placebo-controlled, where SEISMIC was open-label and uncontrolled.

Two things should be said plainly before anyone draws a conclusion from that. The two drugs have never been compared head to head, so any claim that one is more effective than the other is not supported by evidence that exists. And a randomised-withdrawal design answers a different question from an open-label trial: it tests whether patients who have already responded relapse when treatment is removed, which is not the same question as whether treatment produces a response. Comparing a withdrawal result against an open-label response rate is not a comparison at all.

The defensible summary is that relacorilant now has better quality evidence for its own effect than mifepristone has for its, and that this is not the same statement as relacorilant being the better drug. Which matters more in a given patient depends on what is driving the decision, and a patient in whom hypokalaemia or endometrial effects have already forced a change is a different case from one starting treatment.

Where does it sit among the alternatives, and who is it for?

Treatment of Cushing's syndrome is sequenced, and the Endocrine Society clinical practice guideline sets out that sequence. Surgery, usually transsphenoidal for Cushing's disease, is first-line. Medical therapy is used when surgery has failed, is not possible, or while awaiting the effect of radiotherapy. Bilateral adrenalectomy remains definitive for refractory disease and carries its own consequences.

Within medical therapy the choice is between mechanisms rather than between brands. Steroidogenesis inhibitors lower cortisol production and can be monitored biochemically. Pituitary-directed agents act on the corticotroph tumour. Glucocorticoid receptor antagonism blocks cortisol action and cannot be monitored biochemically. The right choice depends on the cause of the hypercortisolism, on which clinical problem dominates, and on what has already been tried and why it was stopped.

Mifepristone's distinctive position is the patient whose dominant problem is hyperglycaemia driven by cortisol excess, in whom surgery has failed or is not an option. That is the indication, and it is also where the mechanism has the most direct effect. It is a poor choice where biochemical monitoring is needed for other reasons, and a difficult one where the patient cannot attend frequent review.

The approved indication is not sex-specific and the trial population included men. The difference in men is the adverse effect profile rather than efficacy: the antiprogestational effects, endometrial thickening and vaginal bleeding, do not apply, while hypokalaemia, oedema and the difficulty of detecting adrenal insufficiency apply unchanged.

Pseudo-Cushing's states, where cortisol is elevated for a reason other than primary cortisol-producing pathology, are a diagnostic problem rather than a treatment one. The indication is endogenous Cushing's syndrome, and the clinical task is distinguishing the two before treating, not treating the former with a drug licensed for the latter.

What should a clinician take from the evidence overall?

Mifepristone occupies a specific and defensible position: a glucocorticoid receptor antagonist for hyperglycaemia secondary to hypercortisolism, after surgery has failed or been ruled out.

Its pharmacology dictates its management, and the list is short enough to hold. Cortisol and ACTH rise and cannot guide titration. Hypokalaemia and oedema follow from unopposed mineralocorticoid activity and are anticipated rather than discovered. Adrenal insufficiency must be recognised clinically because the laboratory will not show it. Anti-diabetic therapy needs reducing as the drug works. Pregnancy is an absolute contraindication. Pituitary disease needs imaging surveillance.

The evidence has real limits and saying so is not a criticism of the drug. The trial behind the approval was open-label, uncontrolled and 24 weeks long in a disease treated for years, and the long-term data is observational. In a rare disease that is a reasonable position to be in, and it is a reason to be precise about what has been demonstrated rather than to overstate it.

A clinician deciding whether to start this drug is really answering three questions. Is hyperglycaemia from cortisol excess the dominant problem, because that is what the evidence addresses. Can this patient attend the frequent review that clinical titration and potassium monitoring require, because without it the drug is unsafe rather than merely unmonitored. And is everyone involved clear that a rising cortisol means it is working, because the alternative is a treatment stopped for the wrong reason.

That last question extends past the prescribing clinician. The cortisol will be seen by a laboratory, possibly flagged, and possibly acted on by someone who was not in the room when the drug was started: an out-of-hours team, a general practitioner, an admitting physician. Writing the explanation into the record where those people will find it is part of prescribing this drug safely, and it is the step most often skipped.

Where can patients find others being treated with Korlym?

A substantial share of the search traffic around this drug is not clinical. People are looking for other patients: support groups, and accounts of what treatment is actually like from those who have had it.

That is a real need and it is not met here. This publication is written for healthcare professionals, and a clinical reference page is the wrong object for someone trying to find out whether the fatigue they are experiencing is normal or whether anyone else found the first month as difficult as they are finding it.

The right destinations are the established patient organisations in this disease area, which run moderated communities

with clinical oversight, and the patient's own endocrinology team, who can answer the specific version of the question rather than the general one. Cushing's syndrome is rare enough that peer contact genuinely matters, and rare enough that unmoderated forums carry a higher than usual risk of confident misinformation.

The risk is specific rather than general here. A patient searching for others on this drug will encounter accounts of rising cortisol described as the treatment failing, because that is the intuitive reading and because the people writing are not endocrinologists. A patient who has been warned in advance that the number goes up and why will read the same thread and recognise it. A patient who has not may stop the drug before their next appointment.

Clinicians reading this can do something useful with that. A patient who has just been started on a drug whose main biochemical marker moves in the counterintuitive direction, and who will read online that rising cortisol means treatment failure, benefits from being told where to look before they go looking.

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