Commentary

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# A Novel Therapeutic Approach for Congenital Adrenal Hyperplasia: Block and Replace?

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## INTRODUCTION

Individuals who have 21-hydroxylase deficiency-related classic congenital adrenal hyperplasia (CAH) need cortisol replacement therapy for the rest of their lives. Patients with the most severe form die in the first few weeks of life from salt-wasting crisis if treatment is not received. Nearly all patients survive because newborn screening programs are now accessible in almost all Western countries and adrenal replacement medication was first introduced 70 years ago. Even after seven decades, the majority of patients still receive hydrocortisone three times a day as part of their medication. The dual therapeutic challenges in CAH are hormone replacement and excess adrenal androgen regulation, especially at night to avoid the early morning surge in adrenal androgens caused by adrenocorticotropin (ACTH). Supraphysiological levels of glucocorticoids are required to achieve the latter, and in certain situations, these doses must be taken in a reverse circadian therapy regimen, with the highest dose given right before bed. Longer-acting synthetic glucocorticoids are frequently used in adult treatment to promote compliance and manage hyperandrogenemia. These medications are given once or twice daily.

**Now that we know, patients experience a variety of early-onset glucocorticoid-associated morbidities**

Early onset of obesity is associated with a greater risk of cardiovascular and metabolic health problems in later life (1). In addition to being 10 cm shorter than anticipated and not reaching their target height, they frequently have low quality of life, reduced fecundity and fertility, and higher mortality rates (1). Current glucocorticoid replacement is unphysiologic in rhythm and excessively high in dose, which contributes to these undesirable results.

Out of an attempt to address the problem, two new therapeutic ideas are emerging. Recently, data on a modified-release hydrocortisone formulation that replicates the typical circadian pattern of cortisol have been released. The phase 3 investigation has shown that testosterone secretion and nighttime 17-hydroxyprogesterone (17OHP) have returned to normal (2). Twice a day, right before bed and right after awakening, the preparation is administered. The major end aim of the trial was not met, since modified-release hydrocortisone only demonstrated superior hormonal control in the morning and was not more effective than conventional glucocorticoid replacement in reducing 17OHP over a 24-hour period.For the best hormonal management, patients typically required supraphysiological glucocorticoid dosages, with an average of 30 mg of hydrocortisone per day. Ongoing safety extension trial data, however, indicates that a gradual dose reduction is feasible without compromising hormonal balance. Because of the short period of the trial (6 months), effects on metabolism or long-term outcome markers of cardiovascular and bone health could not (yet) be shown. The simulation is scheduled to debut in autumn 2021 after receiving a license in Europe.

Since ACTH is the primary cause of adrenal androgen excess, corticotropin-releasing factor type 1 (CRF1) receptor antagonists (3, 4) that limit ACTH secretion offer another strategy to lessen glucocorticoid-associated unfavorable effects. The findings of two phase 2 trials using the second-generation CRF1 receptor antagonist tildacerfont are presented by Sarafoglou et al. (3). A little chemical called tildacerfont binds to the pituitary gland's CRF1 receptors highly and specifically.The goal of tiltacerfont therapy is to lessen the adrenal's ACTH drive, which enables a reduction in supraphysiologic glucocorticoid dosage to just a replacement dose. As of right now, juvenile patients should receive glucocorticoid treatment at doses of 10 to 15 mg/m2, and adult patients should receive hydrocortisone doses comparable to 15 to 25 mg/d (5). A hydrocortisone dose equivalent to 6 to 10 mg/m2 would be a bare replacement dose, which translates to 10 to 20 mg/d in humans. The high prevalence of glucocorticoid-associated morbidities, however, is well explained by the doses that are actually utilized in

Journal of Clinical Endocrinology and Metabolism

practice, according to real-world data from current cohort studies in adults with CAH (6, 7).

In the phase 2 trials that were described, tiltacerfont was well tolerated. In most patients, a once-daily application in the evening decreased ACTH and the subsequent levels of glucocorticoids and androgen precursors. Since there was no discernible dose response in the initial phase 2 study, which involved dose escalation with once or twice daily dosing, lower doses were already effective in blocking ACTH synthesis. A once-daily treatment is effective in lowering or maintaining hormone biomarkers toward normal throughout a 12-week period, according to the second phase 2 research.

In light of these advancements, which patients stand to gain the most from a prospective new block and replace therapeutic concept? Certain patient groupings in particular therapeutic scenarios requiring substantial doses of glucocorticoids, but definitely not all patients. Patients seeking fertility who have testicular adrenal rest tissue are included in this. Currently, in order to stimulate spermatogenesis and induce adrenal rest tissue atrophy, these individuals require overtreatment with doses of adrenal suppressive medication.In a similar vein, progesterone suppression that interferes with endometrial accumulation and ovulation is frequently required by women trying to conceive through supraphysiological dosages.

Treatment can be particularly difficult for developing children and adolescents since controlling hyperandrogenemia may need greater doses of glucocorticoids at the risk of stunting growth. Last but not least, any patient exhibiting cardiovascular and metabolic comorbidities, such as low bone mineral density, obesity, hypertension, or impaired glucose tolerance.

One possible drawback of the medication is that it must be given with a meal of moderate fat for best absorption; ideally, this should happen late in the evening to maximize the suppression of ACTH overnight. This could have the opposite effect on a patient who is obese and has a metabolic risk profile.

The ensuing larger, next-phase trials will have to validate safety and efficacy as well as show the degree of a possible glucocorticoid-sparing impact. In the future, it may be possible to combine block and replace with a unique hydrocortisone formulation that has been circadianly adjusted.

The best patient care in CAH cannot be achieved with more of the same therapy as in previous decades, according to the data. Without a doubt, the recently developed treatments pave the way for the necessary shift toward a more customized and physiological approach to care that will maximize long-term patient outcomes in CAH.

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