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LATEST ADVANCES FOR TREATING CONGENITAL ADRENAL HYPERPLASIA DUE TO 21-HYDROXYLASE DEFICIENCY

21-HİDROKSİLAZ EKSİKLİĞİNE BAĞLI KONJENİTAL ADRENAL HİPERPLAZİ TEDAVİSİNDEKİ YENİLİKLER

Ecesu ÇETİN[1], Mehmet Furkan BURAK[2,3]

[1]Harvard Medical School, Brigham and Women's Hospital, Division of Endocrinology, Diabetes and Hypertension, Postdoctoral Research Fellow, Boston, MA, United States
[2]Harvard Medical School, Brigham and Women's Hospital, Division of Endocrinology, Diabetes and Hypertension, Principal Investigator, Boston, MA, United States
[3]Harvard T.H. Chan School of Public Health, Department of Molecular Metabolism, Boston, MA, United States

ORCID IDs of the authors: E.Ç. 0000-0001-7682-3597; M.F.B. 0000-0001-6222-1552

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ABSTRACT

Congenital adrenal hyperplasia (CAH) is a group of inherited diseases characterised by disrupted glucocorticoid (GC) and mineralocorticoid (MC) synthesis in the adrenal glands. Most cases are caused by 21-hydroxylase (21-OH) enzyme deficiency, which leads to diminished cortisol and aldosterone levels, a reactional increase in adrenocorticotropic hormone (ACTH), resulting in excessive adrenal androgen production. CAH is a challenging condition that often requires supraphysiological doses of GCs to suppress ACTH and subsequent androgen production. It can lead to complications such as short stature and premature puberty during childhood, hyperandrogenism, infertility, and iatrogenic Cushing syndrome in adulthood. This manuscript reviews the current therapeutic landscape, unmet needs, and emerging therapies for CAH, including corticotropin-releasing factor type 1 (CRF1) receptor antagonists, ACTH inhibitors, and investigational gene therapies to replace 21-OH enzymatic activity. The main focus of the pipeline agents is to reduce androgen levels and the need for supraphysiological dosing of GCs. Crinecerfont, a CRF1 receptor antagonist, has recently been approved by the Food and Drug Administration (FDA) after showing significant improvements in androgen levels in adults and paediatric patients aged 4 years and older with classic CAH. The manufacturer claims it is the first novel CAH treatment in 70 years. However, it failed to maintain low androgen levels while reducing GC dosing. Hence, further pipeline is investigating whether it is possible to achieve both goals or cure the disease. The long-term safety and efficacy of these promising

ÖZET

Konjenital adrenal hiperplazi (KAH), adrenal bezlerde glukokortikoid (GC) ve mineralokortikoid (MC) sentezinin bozulmasıyla karakterize bir grup kalıtsal hastalığı ifade eder. Vakaların büyük çoğunluğu, kortizol ve aldosteron seviyelerinin azalmasına yol açan, buna bağlı olarak adrenokortikotropik hormon (ACTH) düzeylerinde reaksiyonel bir artışla adrenal androjen üretiminin fazlaca artmasına neden olan 21-hidroksilaz (21-OH) enziminin eksikliğinden kaynaklanır. KAH, genellikle ACTH'yi ve buna bağlı androjen üretimini baskılamak için fizyolojik sınırların üzerinde GC dozlarının kullanımını gerektiren, yönetimi zor bir hastalıktır. Bu durum, çocukluk döneminde kısa boy ve erken ergenlik, yetişkinlikte ise hiperandrojenizm, infertilite ve iyatrojenik Cushing sendromu gibi komplikasyonlara yol açabilir. Bu makale, KAH için mevcut tedavi seçeneklerini, tedavi alanındaki eksiklikleri ve gelişmekte olan yeni tedavi yaklaşımlarını kapsamlı bir şekilde ele almaktadır. Bunlar arasında kortikotropin salıcı faktör tip 1 (CRF1) reseptör antagonistleri, ACTH inhibitörleri ve 21-OH enzimatik aktivitesini yerine koymayı hedefleyen deneysel gen tedavileri bulunmaktadır. Yeni geliştirilen ajanların ana hedefi, androjen seviyelerini azaltmak ve suprafizyolojik GC dozlarına duyulan ihtiyacı en aza indirmektir. CRF1 reseptör antagonisti olan crinecerfont, androjen seviyelerinde önemli iyileşmeler göstermesi nedeniyle; 4 yaş ve üzeri çocuk ve yetişkin klasik KAH hastalarında kısa bir süre önce Amerikan Gıda ve İlaç Dairesi (FDA) tarafından onaylanmıştır. Üretici firma, bu ilacın son 70 yıl içerisinde onaylanan ilk yenilikçi KAH tedavisi olduğunu öne sürmektedir. Ancak, bu tedavi yöntemi, GC dozlarını azaltırken düşük androjen seviyelerini sürdürebilme hedefini karşılayama-

Corresponding author/İletişim kurulacak yazar: Mehmet Furkan BURAK – mfburak@hsph.harvard.edu

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therapeutic approaches require further investigation and elucidation.

Keywords: Congenital adrenal hyperplasia, 21-hydroxylase, melanocortin type 2 receptor, CRF receptor type 1, gene therapy

mıştır. Bu nedenle, güncel araştırmalar, her iki hedefe aynı anda ulaşılıp ulaşılamayacağı veya hastalığın tamamen tedavi edilip edilemeyeceği sorularına yanıt aramaktadır. Bu umut verici tedavi yaklaşımlarının uzun vadeli güvenliği ve etkinliği daha fazla araştırma ile kapsamlı bir şekilde değerlendirilmelidir.

Anahtar Kelimeler: Konjenital adrenal hiperplazi, 21-hidroksilaz eksikliği, melanokortin tip 2 reseptörü, kortikotropin salgılatıcı faktör, gen terapisi

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of inherited diseases that are characterised by the disruption of physiological cortisol and aldosterone synthesis in the adrenal glands. A deficiency in the 21-hydroxylase (21-OH) enzyme causes more than 95% of CAH cases (1). This leads to decreased negative feedback to the Hypothalamic-Pituitary-Adrenal (HPA) axis (Figure 1) (2). This form of CAH is the primary focus of this review.

Diminished serum cortisol levels in patients with 21-OH deficiency trigger a compensatory increase in the pituitary secretion of adrenocorticotropic hormone (ACTH). This, in turn, promotes hyperstimulation of the adrenal gland, resulting in hyperplasia. ACTH-dependent overstimulation of the adrenal gland shifts steroid synthesis to excessive androgen production in a setting of 21-OH deficiency (3). The clinical manifestations vary greatly depending on the severity of the enzymatic defect and the degree of androgen excess. 21-OH deficiency-associated CAH is mainly categorised into classic and non-classic subtypes. The classic form is a severe and potentially life-threatening disorder that arises from a lack of both cortisol and aldosterone. If untreated, the classic form can be fatal due to adrenal crises during the initial two weeks after birth. Additionally, with some enzymatic activity, patients may exhibit ambiguous genitalia at birth, as well as clinical manifestations of hyperandrogenism resulting from early adrenarche and gonadotropin-independent precocious puberty. These manifestations often include the premature appearance of pubic hair and rapid growth progression (4). Non-classic CAH represents a less severe form of the condition, arising from genetic mutations that preserve 20–50% of 21-OH activity. It is frequently asymptomatic but may occasionally exhibit signs of androgen overproduction in females. When present, the symptoms typically emerge during childhood or early adulthood, resulting in a less immediate diagnosis compared with classic CAH (4, 5). 21-OH deficiency is a common genetic condition (1). Its prevalence differs significantly across different demographic groups and regions, ranging from as rare as 1 in 28,000 to as common as 1 in 280 (6, 7).

The diagnosis of CAH typically begins with newborn screening to enable an early identification of affected individuals. Beyond infancy, the initial evaluation in symptomatic patients often includes measuring early-morning serum 17-hydroxyprogesterone (17-OHP) levels. This approach is adopted because 21-OH, the enzyme responsible for converting 17-OHP into cortisol and aldosterone precursors, is deficient in most cases of CAH. As a result, the absence of 21-OH activity leads to the accumulation of 17-OHP, making its measurement a key diagnostic marker for the condition. If the initial 17-OHP measurement is inconclusive, it is advised to evaluate for potential deficiencies in other enzymes. Genetic testing is generally reserved for inconclusive results, unreliable tests, or counselling (8). Once the diagnosis is established, the primary goals of management are to prevent adrenal crises through a balanced hormone replacement therapy, normalise adrenal androgen production, and ensure appropriate physical and sexual development for children. For the treatment of CAH in children, hydrocortisone is the preferred therapy. Suspension forms of hydrocortisone, as well as long-acting potent glucocorticoids (GCs), are not recommended due to their effects on the suppression of growth (2, 8). In infancy, fludrocortisone and sodium chloride supplements are incorporated in addition to GCs. The treatment regimen in adults includes hydrocortisone and/or long-acting GCs, supplemented with mineralocorticoids (MCs) where needed (8). Additionally, modified-release hydrocortisone, approved in the United Kingdom and Europe but not in the US, has demonstrated some potential therapeutic benefits (9, 10). However, achieving adequate suppression of the HPA axis often necessitates GC dosages that exceed physiological levels. Otherwise, insufficient suppression of ACTH secretion can result in hyperstimulation of the adrenal gland and hyperandrogenism (5, 11). Maintaining the appropriate balance of GC treatment is challenging, as excess doses can lead to iatrogenic Cushing's syndrome or inadequate GC dosing can lead to hyperandrogenism. Consequently, the therapeutic window for GC replacement is significantly narrower compared with other forms of adrenal insufficiency without concomitant androgen excess (2, 3, 5, 11). This review examines the limitations of current treatments for CAH and explores promising emerging therapies.

An overview of the HPA axis

The HPA axis is a complex neuroendocrine system that regulates vital functions. These include the secretion of

stress hormones and the production of sex hormones. It also coordinates metabolism and maintains homeostasis (12). This important axis is a direct drug target for CAH treatment (Figure 1). Corticotropin-releasing factor (CRF), also referred to as corticotropin-releasing hormone (CRH), is a peptide hormone that is mainly responsible for regulating the HPA axis (13). Neurosecretory parvocellular neurons of the paraventricular nucleus of the hypothalamus release CRF into the hypothalamohypophyseal portal system (12). The physiological actions of CRH are mediated through two distinct receptor subtypes, CRF-1 and CRF-2. CRF-1 is primarily expressed centrally, serving as the main receptor subtype responsible for mediating the endocrine stress response of CRH. The binding of CRF to CRF1 on the anterior pituitary stimulates ACTH production from its precursor protein, proopiomelanocortin (POMC), and its subsequent secretion into the systemic circulation (12, 13). Circulating ACTH targets the adrenal cortex, where it binds to the melanocortin type 2 receptor (13). This activation promotes the secretion of corticosteroids from the zona fasciculata, MCs from the zona glomerulosa, and androgens predominantly from the zona reticularis (12). This HPA axis is regulated through negative feedback mechanisms involving GCs, which are impacted by their concentration, duration, and rhythmic release patterns (12, 13). Additionally, the HPA axis can be regulated by CRH-binding proteins commonly present in the circulation and expressed in the pituitary and hypothalamus (12). If this negative feedback mechanism is impaired, such as in the case of CAH due to the inability to synthesise corticosteroids, ACTH exerts chronic stimulation in the adrenal cortex and promotes hyperplasia.

Treatment landscape for CAH and management challenges

Current CAH management is associated with numerous adverse outcomes. These complications arise from either undertreatment of the disease, excessive adrenal androgen levels, or the supraphysiological administration of GCs and MCs to suppress the HPA axis (5). CAH management is particularly challenging in the paediatric population due to the intricate balance required between dynamic growth patterns and premature sexual development. In paediatrics, hydrocortisone is the preferred short-acting GC; however, its rapid clearance often results in periods of androgen rebound between doses (8, 14). Inadequate management in boys can lead to central precocious puberty, while in girls, it may result in delayed puberty (15). Both excessive GC therapy, leading to growth suppression, and insufficient GC therapy, resulting in elevated androgen levels accelerating skeletal development prematurely, impair final adult height attainment (4, 5). In adulthood, males typically do not seek medical help. In contrast, females mostly seek help primarily for hyperandrogenism and infertility and often end up experiencing GC overdosing. In the long term, affected individuals are at an elevated risk of a broad spectrum of multisystem complications. Cardiovascular and metabolic risks are significantly elevated, characterised by higher rates of obesity, insulin resistance, hypertension, dyslipidemia, and cardiovascular disease (16, 17). Bone health is frequently compromised due to prolonged GC therapy, leading to microarchitectural alterations, increased fracture susceptibility, and osteoporosis (4, 18, 19). Additionally, the hypersecretion of ACTH not only drives adrenal hyperplasia but may also predispose individuals to adrenal tumour development over time (5, 20). Gonadal dysfunction is another significant concern, presenting as hypogonadotropic hypogonadism and infertility, while excess adrenal androgen levels in females may lead to additional manifestations such as acne, hirsutism, irregular menstrual cycles, and voice deepening (4, 5, 21). In males, elevated ACTH could contribute to testicular adrenal rest tumours (TART), which results in gonadal dysfunction (21). These challenges demonstrate the critical need to develop innovative therapeutic strategies that can mitigate the long-term effects and enhance the overall outcomes for individuals living with CAH.

Evolving treatment pipeline for CAH

Novel therapeutic approaches are being explored in CAH to further improve outcomes for patients as well as reduce excessive GC and androgen exposure. These newer strategies target the hypothalamic–pituitary–adrenal axis through alternative mechanisms and provide more effective management options for patients. Figure 1 demonstrates an overview of the hypothalamic–pituitary–adrenal axis and the targets of emerging therapies (Figure 1). In summary, these agents target the ACTH and consecutive overstimulation of the adrenal gland. Multiple ACTH inhibition approaches have emerged. They either decrease the secretion via CRF1 antagonism or directly inhibit ACTH through antibody neutralisation or ACTH receptor antagonism. These approaches aim for better disease management and control of androgen levels while continuing GC and MC therapy. The ultimate cure for the disease is to restore enzyme activity, which is also under development.

CRF1 receptor antagonists

Crinecerfont

Crinecerfont is an oral CRF1 receptor antagonist that offers a nonsteroidal approach to managing 21-OH deficiency (Figure 1) (22, 23). In a Phase II trial with adults, crinecerfont demonstrated substantial, dose-dependent reductions in ACTH, 17-OHP, and androstenedione levels. It also decreased the testosterone levels in female patients and reduced the androstenedione/testosterone ratio in the male. Remarkably, these effects occurred in the early morning, which is a notoriously difficult period for attaining effective disease management with physio-

logic GC regimens (22). Following this, another Phase II study in adolescent participants demonstrated comparable results, which is an important step for early intervention to support healthy development (24).

The CAHtalyst phase 3 trial included 182 participants (2:1 crinecerfont 100 mg vs placebo twice per day) across 54 international centres. The study involved a 24-week treatment period, beginning with 4 weeks of stable GC dosing to assess androstenedione reduction. During this initial phase, crinecerfont significantly decreased androstenedione concentrations (-47% active arm vs +7.7% for placebo). The following 20 weeks focused on GC dose optimisation to achieve the lowest dose while maintaining androstenedione control. By week 24, GC doses were reduced by 27.3% in the crinecerfont group compared with 10.3% in the placebo group. Notably, 62.7% of participants in the crinecerfont group reached physiological GC levels with androstenedione control, compared to 17.5% in the placebo. There was no increase in the incidence of adrenal crises. The commonly observed side effects were headache and fatigue (23). Similar benefits were demonstrated in the paediatric population. In a phase 3 study involving 103 paediatric participants, crinecerfont decreased androstenedione levels by 6.9 nmol/litre by week 4, while levels were elevated by 2.5 nmol/litre in the placebo. Crinecerfont reduced the GC dose by 18.0% to physiological levels while still controlling androstenedione levels. In comparison, the placebo group experienced a 5.6% increase in the GC dose (14). The results show that crinecerfont therapy enabled meaningful decreases in GC doses to physiological levels or decreases in androgen levels with stable GC dosing in both paediatric and adult patients with classic CAH. However, once GC doses were reduced in the phase 3 trial, there was a rebound increase in androgen levels. Further investigation is needed to determine if crinecerfont could lower GC doses to levels necessary for intensive management (23). Importantly, in December 2024, The U.S. Food and Drug Administration (FDA) granted approval for crinecerfont for use in conjunction with GCs in adult and paediatric patients aged 4 years and above diagnosed with CAH (25). This approval was focused solely on hyperandrogenism, rather than lowering GC doses.

Tildacerfont

Tildacerfont is an orally administered second-generation antagonist of the CRF1 receptor (Figure 1). It attaches selectively to CRF1 receptors located in the pituitary gland and has a strong affinity. Initially, it was proposed as a once-daily dosing regimen to differentiate it from Crinecerfont, which requires a twice-daily regimen. Two Phase 2 trials have demonstrated that tildacerfont might decrease the levels of ACTH, 17-OHP, and androstenedione in individuals with inadequately managed CAH. The initial study established a proof-of-concept through the decrease in ACTH, and the results of the subsequent study further corroborated these findings. Patients with poorly controlled CAH at baseline experienced marked improvements in biomarkers while maintaining a stable dose of GC treatment, with some even reaching ACTH and androstenedione normalisation. However, in both studies, patients with a well-controlled disease only had slight biomarker improvements. Hence, their studies failed to show a robust efficacy. Longer-term studies will be needed to assess the clinical endpoints and the possibility of lowering GC dosages. Another concern is that tildacerfont was found to interact with dexamethasone, a commonly used medication in adult CAH management (26).

ACTH antagonists

Atumelnant (CRN04894)

Atumelnant (CRN04894) is a nonpeptide orally bioavailable small molecule. It is a potent and subtype-selective first-in-class antagonist of the ACTH receptor (27, 28). Atumelnant acts on the melanocortin 2 receptor (MC2R) located in the adrenal cortex (Figure 1). It inhibits the action of ACTH on this receptor and disrupts the downstream signaling cascade (28). In a placebo-controlled study of healthy participants, administering 80 mg of atumelnant once-daily for 10 days reduced the average 24-h serum cortisol by 51% and androstenedione levels by 40%, despite an approximately fivefold elevation in the 24-h average ACTH levels. Furthermore, the median 24-h urinary-free cortisol was reduced by 75% (29). Expanding upon these results, an ongoing phase 2 dose-finding study has been evaluating atumelnant in 30 adult patients with CAH (30). The preliminary findings indicate that a once-daily dose of 120 mg for 12 weeks led to an 80% reduction in androstenedione levels and a 65% decrease in 17-OHP concentrations (31). In contrast to the findings

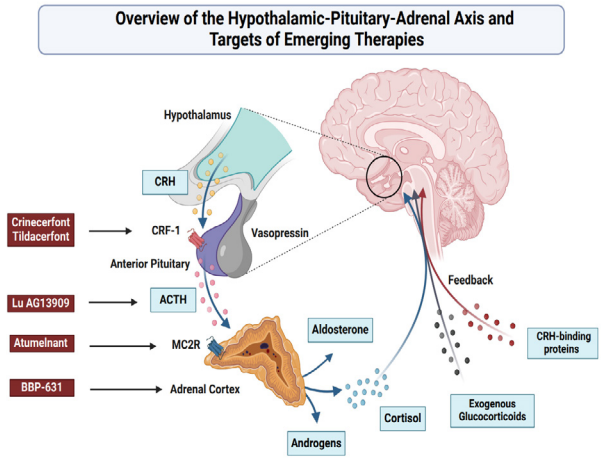

Figure 1: The figure depicts the hypothalamic–pituitary–adrenal axis and the targets of the novel emerging therapies

from the healthy participant trial, ACTH levels did not significantly change in patients with CAH (32). Remarkably, eight out of 13 female participants with elevated baseline testosterone levels achieved normalisation by week 12. Additionally, six of eleven affected female patients experienced a return of their regular menstrual cycles. The study also reported a significant decrease in the adrenal gland volume and androgen-related polycythaemia resolved in five of six affected participants (31). Overall, atumelnant was tolerated well. The most frequently reported adverse events were headache and fatigue (31, 32). These results are promising for its potential use for treating CAH.

Lu AG13909

Lu AG13909 is an IgG1 monoclonal antibody that targets ACTH with high affinity and specificity, thereby interrupting MC2R signaling (Figure 1) (33, 34). Taking this further, a Phase 1 study of Lu AG13909 is undergoing to evaluate its safety profile, tolerability, and efficacy. The study is being conducted in adult patients with CAH who have baseline elevated 17-OHP concentrations and are on a stable GC and MC regimen. Each participant receives up to six doses of intravenous Lu AG13909 over 28-to 35-day intervals (33, 35). Moreover, a Phase 2 trial is assessing the effects of Lu AG13909, administered both intravenously and subcutaneously, on cortisol concentrations in adult patients with Cushing's disease (36).

Gene therapy: BBP-631

BBP-631 is an investigational gene therapy using an AAV5 capsid serotype (AAV5) vector to deliver a functional copy of the single-stranded DNA of the human CYP21A2 transgene (Figure 1). This gene encodes the 21-OH enzyme (37, 38). In a CAH mouse model of 21-OH deficiency, BBP-631 therapy demonstrated early and durable effects in correcting the enzyme deficiency. It also achieved persistent human CYP21A2 gene expression in the adrenal cortex of non-human primates (37). Previous studies demonstrated that the correction of adrenal function was transient in animal models. These findings, along with the limitations of preclinical studies, raised concerns that advancing to clinical trials of gene therapy for CAH might have been premature (39). The Phase 1/2 study revealed that individuals with CAH could produce endogenous cortisol levels up to 11 µg/dL following the administration of BBP-631. Biochemical improvements supported the sustained effect of gene therapy. These included lasting elevations in the product of 21-OH, 11-deoxycortisol, which increased up to 99 times the baseline levels. The results demonstrated the promising potential of gene therapy for treating CAH. However, they did not meet the threshold required to continue investing in and developing BBP-631 for CAH, leading to the discontinuation of this program (40). This initial effort proved that CAH patients with complete 21-OH deficiency could synthesise their own cortisol and that gene therapy could be safely administered. This approach requires long-term development efforts for dosing, duration optimisation, and long-term safety evaluation.

DISCUSSION

CAH is a significantly challenging and common endocrine disorder affecting both paediatric and adult populations. The current standard of care includes different formulations of GC and MC replacement with limited efficacy on ACTH and subsequent androgen level suppression. In adults, males generally do not seek much help and tend to lose follow-up. Females primarily seek help with infertility and hyperandrogenism. In the paediatric population, the unmet need is even higher with challenging growth and sexual development complications regardless of gender. Recently, there have been great efforts to increase awareness and willingness to treat rare genetic disorders. CAH is one of the most common genetic disorders, which is included in newborn screening. Recent efforts for drug development against CAH have focused on ACTH inhibition and hyperandrogenism with the hope of reducing GC dosing to prevent iatrogenic Cushing syndrome. Recently, crinecerfont was approved by the FDA to lower androgen levels in CAH and has been recorded as the first approved drug for any rare disorder in the last 70 years (41). This is a very encouraging development for the entire rare disease field. Even though crinecerfont offers a very promising and safe approach to lower androgen levels, it failed to achieve both the initial goals of lowering GC and androgen levels at the same time. The use of crinecerfont allowed for the reduction of GC doses to physiological levels (14, 22-24). It also effectively reduced androstenedione levels in two Phase 2 trials (22, 24). However, in the subsequent Phase 3 trial involving adults, the average androstenedione levels increased from 316 ng/dL to 607 ng/dL after the reduction of GC doses (23). The fact that average androgen levels only dropped by around 50% (not fully normalised) and that lowering GC doses caused rebound elevations suggests that the trialled regimen of 100 mg twice daily was perhaps not enough for maximum efficacy. The question remains whether the field will try higher doses in separate trials or pursue off-label use for severe cases. At the same time, any potential increase in adverse effects from dose escalation would need to be carefully evaluated. For now, this regimen adds two more pills to the patients' daily routine without decreasing the GC and MC doses. Hence, some patients might struggle with compliance due to the pill burden. Given the significant economic cost of the treatment, consideration should be given to individual patients and treatment goals when using crinecerfont in a hyperandrogenism-centric manner. We should also consider that the most common side effects of crinecerfont are fatigue, headache, dizziness, and low

appetite (42). These side effects are already bothersome for CAH patients with fluctuating GC dosing and overlap with the symptoms of adrenal insufficiency. Males with TART or females seeking help for infertility due to hyperandrogenism would be a prioritised special group to be treated, yet the potential outcome remains uncertain.

In another aspect, crinecerfont showed similar trends in insulin sensitivity and body weight across adult and paediatric trials. In adults, reductions in prolonged high-dose GC therapy improved weight and insulin sensitivity. However, these changes did not reach statistical significance. It is worth noting that these outcomes were secondary endpoints, and the 24-week duration of the trial may have been insufficient for a full assessment (23). Supporting this, in the paediatric trial, notable improvements in BMI and insulin resistance were observed. This occurred despite the limited duration of GC dose reduction (14). Variations in GC dose changes within the placebo groups may explain the discrepancy in statistical significance between the adult and paediatric populations. In the adult trial, the placebo group also reduced their GC dose, albeit less than the crinecerfont group. This potentially diminished the contrast between the two groups (23, 43). Conversely, in the paediatric trial, the placebo group slightly increased their baseline GC dose (14).

In summary, crinecerfont would be utilised significantly for hyperandrogenism, but atumelnant could offer some advantages with once-daily dosing and more direct inhibition of ACTH via its end-organ receptors (Figure 1). Atumelnant has also been evaluated for ACTH-dependent Cushing's syndrome and showed strong inhibition of ACTH despite very high circulating levels (4045 pg/mL) in an early Phase 1 trial (29, 44). It could be harder to lower actual ACTH synthesis and secretion but more likely to block its receptors. This approach might overcome the rebound elevation of androgens seen with crinecerfont, given its strong blockage of ACTH receptors. The mechanistic basis of its effectiveness is mediated by the selective antagonism of MC2R. Notably, this receptor is only expressed in the adrenal cortex (27, 45). Such specificity establishes its antagonism as a potentially optimal therapeutic strategy. Another promising finding from the initial results of the Phase 2 study is the improvement in androgen-mediated polycythaemia in most affected participants (31). This may reduce the cardiovascular risk, which is an important long-term complication for individuals with CAH (16, 17, 46). Additionally, the data showing that 55% of affected women experienced spontaneous return of their menses is promising for infertility indication. However, its true clinical impact will depend on outcomes from advanced trials, particularly Phase 3 studies, which aim to determine whether sufficient androgen suppression can be achieved under reduced GC dosing. One important point for consideration is the homology MC2R shares with other melanocortin receptors, specifically 45% with MC3R and 38% with MC4R (27, 47). Off-target binding appears less likely given these low homology rates and its target specificity. However, this is particularly concerning because of the risk of adverse effects mediated through MC3R or MC4R activation, which would affect food intake and energy expenditure. Although ACTH elevation was observed in the Phase 1 study (29), no such increase was seen in the initial results of the Phase 2 study (32). It will be important to monitor whether ACTH elevation occurs in the remaining Phase 2 and upcoming Phase 3 trials. If persistent ACTH elevation is noted in subsequent studies, the potential downstream effects, including the risk of hyperpigmentation, will require careful evaluation (48). The consequences of elevated, long-standing circulating ACTH levels are unknown in the setting of blocked MC2R. Some literature indicates adrenal gland-independent effects of ACTH, which will require careful consideration in the long term (49). In summary, a comparison with simulations from the stoichiometry of atumelnant dose-response studies suggests that the ACTH increase in a setting of lower GC dosing might not result in a rebound increase in androgen levels if MC2R is fully or mostly blocked. This approach could address the current unmet need of lowering both GC doses and androgen levels simultaneously.

Another emerging therapy, Lu AG13909, represents a first-in-class anti-ACTH monoclonal that disrupts MC2R signaling (33). Unlike atumelnant, it neutralises ACTH-driven signaling across all five melanocortin receptor subtypes (34). This raises concerns about potential unintended adverse effects from interactions with melanocortin receptors other than MC2R. Future clinical trials will need to carefully evaluate this possibility.

Finally, although gene therapy treatments represent the most promising approach with their potential to provide a curative solution, the development of BBP-631 has been discontinued by the manufacturing company (40). Regrettably, the regenerative nature of the adrenal cortex poses a significant challenge for achieving sustained benefit with recombinant adeno-associated viral vector gene therapy for CAH. The constant cellular renewal within the adrenal gland makes it difficult to maintain genetic modifications over the long term (50). Overcoming this physiological barrier may require innovative strategies to realise the full potential of gene therapy. However, findings from the trial reported increased cortisol production and durable BBP-631 transgene activity. These findings show that the challenge may be surmountable (40). Recent advancements in gene editing technologies might help create alternative strategies for AAV gene delivery. Moving forward, further studies will provide guidance in understanding the efficacy and durability of gene therapies.

CONCLUSION

The management of CAH due to 21-OH deficiency remains a significant challenge, as current treatments, though effective, are suboptimal and linked to long-term adverse outcomes. Pipeline therapies, such as ACTH and CRF1 receptor antagonists, demonstrate the potential to normalise adrenal androgen levels without requiring supraphysiological GC doses. We recommend that clinicians educate their patients about the long-term risks of GC overdose, prefer hydrocortisone, and attempt to titrate down to physiological doses. An additional night-time dose of dexamethasone, a long-acting GC, is commonly used for ACTH suppression but contributes to GC-related harm. Instead, clinicians should consider using novel agents such as crinecerfont to lower androgen levels. Treatment goals should be personalised, and patients should be informed about newer treatments. Higher doses of crinecerfont have not been tested, leaving an open question for researchers. Atumelnant has promising early data but has not been tested in a setting of lowered GC dosing; hence, more investigation is needed in a timely manner. These newer agents are expensive and require insurance authorization. Therefore, advocacy for access is also critical. Moreover, gene therapies hold curative potential but require more collective efforts to bring them into clinical practice. Importantly, the long-term safety and efficacy of these emerging approaches remain to be fully elucidated.

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