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Letter to the Editor

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EMERGING THERAPEUTIC STRATEGIES IN CONGENITAL ADRENAL HYPERPLASIA: A COMMENT ON “LATEST ADVANCES FOR TREATING CONGENITAL ADRENAL HYPERPLASIA DUE TO 21-HYDROXYLASE DEFICIENCY”

KONJENİTAL ADRENAL HİPERPLAZİDE GELİŞMEKTE OLAN TEDAVİ YAKLAŞIMLARI: “21-HİDROKSİLİZ
EKSİKLİĞİNE BAĞLI KONJENİTAL ADRENAL HİPERPLAZİNİN TEDAVİSİNDE YENİLİKLER” BAŞLIKLIL
DERLEMELERE BİR YORUM



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Dear Editor,

We read with great interest the review article entitled “Latest advances for treating congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency” by Ecesu Çetin and Mehmet Furkan Burak, published in Volume 88, Issue 2 of your journal dated April 28, 2025. We thank the authors for emphasising new therapeutic approaches that may help overcome the challenges of treating CAH. Based on the review, we would like to highlight several noteworthy points.

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency exhibits a variable clinical spectrum depending on the enzyme activity and gender. The current treatment approach consists of hydrocortisone for children, hydrocortisone and long-acting glucocorticoids for adults, and mineralocorticoid supplementation when clinically indicated. However, the inability to fully mimic physiological cortisol secretion and the limitations of individualised dosing remain major drawbacks. Balancing the risks of under treatment and the adverse effects of supraphysiologic doses continues to be a challenge for both physicians and patients. Therefore, the search for safer and more effective treatment alternatives remains essential (1).

Modified-release hydrocortisone preparations designed to better replicate physiological cortisol secretion have been approved for

use in several countries. Continuous subcutaneous hydrocortisone infusion via a pump has also been explored as a treatment option, although it remains impractical in daily use (2). Since the early 2000s, advances in understanding steroid biosynthesis and genotyping technologies have accelerated the development of new therapeutic strategies that are more physiological, have fewer side effects, and offer greater efficacy (3). Targeted drugs acting on steroidogenic pathways and gene therapy have emerged as promising approaches.

The FDA approval of Crinecerfont, a corticotropin releasing hormone receptor-1 (CRF-1) antagonist, in 2024 represents a significant milestone. However, the reduction of androgen levels following glucocorticoid dose reduction—a key therapeutic goal—may limit its long-term integration into standard therapy. Another CRF-1 receptor antagonist mentioned in the review, Tildacerfont, was discontinued because of unsuccessful outcomes (4).

Phase 2 trials of the Adrenocorticotrophic hormone (ACTH) receptor antagonist Atumelnant and Phase 1 studies of the monoclonal antibody Lu AG13909 are ongoing (4). Close attention should be paid to the results of these trials, as the long-term safety and efficacy outcomes will determine their role in clinical practice.

In gene therapy, CYP21A2 expression was demonstrated in nonhuman models with BBP-631, the first such attempt in CAH. Although the



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study was terminated, it remains an important milestone for future gene therapy designs (4).

Stem cell-based therapy is another field of interest. Advances in cellular technologies have raised the question of whether an approach similar to haematopoietic stem cell therapy could be feasible for adrenal tissue, and several modelling studies have been initiated. Protocols using induced pluripotent stem cells (iPSCs) or mesenchymal stem cells (MSCs) have been developed. These strategies hold promise not only for transient hormonal balance but

also for generating functional adrenal cortex tissue, offering potential long-term solutions (4, 5). However, technical and economic limitations that clinical application will require time.

In conclusion, there remains a need for individualised therapies that can mimic physiological cortisol secretion and provide long-term safety and stability in CAH management. Advances in biotechnology may herald a transformative era for CAH treatment.



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