Tian, Adv Cancer Prev 2022, 6:6

Advances in Cancer Prevention

ISSN: 2472-0429

Mini Review Open Access

Oestrogen Conversion During cycle with External Testosterone

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Abstract

Treatment options that directly address the hyper-cortisolemia include surgery, medical treatment, and/or radiotherapy. Each option has its drawbacks; for instance, radiation techniques become fully effective only after a prolonged period of time and medical treatment, as a bridge is necessary.

Keywords: Adrenalectomy; Steroidogenensis inhibitors; Imidazole; Off-label treatment; Medication;

Introduction

Focusing more specifically on Cushing's disease, the most frequent etiology of CS, Endocrine Society Clinical Practice Guideline recommends surgical resection of the pituitary lesion as a first line of treatment, unless surgery is contraindicated or unlikely to successfully reduce excess cortisol levels. For patients for whom disease was not controlled by initial surgery, or for patients with severe, life-threatening disease, bilateral adrenalectomy is also an option. However, as a result of the adrenal insufficiency induced by bilateral adrenalectomy, patients undergoing the procedure will require hydrocortisone replacement and have an increased risk of adrenal crises during their lifetime. Medical treatment is recommended in patients who are not surgical candidates, or for whom surgery has failed, and in patients awaiting the effects of radiation therapy. There are three specific targets for medical therapy in CD, the corticotroph tumor, adrenal steroidogenesis inhibitors, and glucocorticoid receptor blockers [1]. Steroidogenesis inhibitors are recommended by the Endocrine Society as second-line treatment after adrenomectomy in CD, depending on clinical circumstances; as first-line treatment for patients with ectopic adrenocorticotropic hormone secretion when a tumor is not detected; or as an adjunct treatment for patients with adrenocortical carcinoma. Corticotropin stimulates steroidogenesis by the adrenal glands. Through a variety of enzymatic reactions, cholesterol, the common steroid precursor, is converted to aldosterone, cortisol, or androstenedione. Adrenal steroidogenesis inhibitors, which act by blocking various steps in the steroid biosynthesis pathway resulting in reduced production of cortisol and other steroids, are a cornerstone of medical treatment of CS. This review summarizes the key features of different adrenal steroidogenesis inhibitors for the treatment of CS, with particular emphasis on steroidogenesis inhibitors currently in clinical development. Ketoconazole, a synthetic imidazole derivative, is an antifungal that, at higher doses, reduces adrenal steroid production. However, due to liver toxicity, the approved use of ketoconazole in the United States is restricted to the treatment of serious fungal infections with no other viable treatment options. Ketoconazole is approved for the treatment of CS in the European Union. While not approved for the treatment of CS by the US Food and Drug Administration, ketoconazole is one of the most commonly used steroidogenesis inhibitors for off-label treatment of CS. Ketoconazole inhibits key cytochrome P450 (CYP) enzymes involved in multiple steps of steroidogenesis in the adrenal cortex, including CYP17A1, CYP11A1, CYP11B1, and CYP11B2. Ketoconazole is a racemic mixture of 2S, 4R and 2R, 4S enantiomers, and these enantiomers exhibit differences in inhibitory potency for the enzymes involved in steroidogenesis [2]. Ketoconazole has also been reported to directly inhibit ACTH secretion, although these findings have not been confirmed. In patients with CS, ketoconazole treatment has been associated with significant decreases in urinary free cortisol (UFC) and urinary levels of cortisol and androgen metabolites. A retrospective study of patients receiving single-agent ketoconazole reported that the patients had normal UFC at the end of the study, while uncontrolled patients had decrease in UFC; concurrent improvements in hypertension, diabetes, and hypokalemia were also observed. Escape from ketoconazole-mediated control occurred in some patients. However, interestingly, patients treated for more than 2 years remained controlled with a stable dose of ketoconazole. Elevations in liver enzymes occurred in of patients treated with ketoconazole. Liver enzyme levels returned to normal in weeks after lowering the dose or discontinuing treatment, and severe drug-induced liver injury was rare. In this retrospective analysis, no fatal hepatitis was observed; however, a dramatic increase in liver enzymes was observed in one patient who was consuming concomitant alcohol and high-dose acetaminophen. Similarly, in retrospective chart review, elevation of liver enzymes and severe acute liver injury were rarely observed with ketoconazole treatment. Concomitant use of drugs with known hepatotoxic effects should be avoided, and acid-lowering drugs should be used with caution, as they decrease the efficacy of ketoconazole. Adrenal insufficiency is rare, except when the treatment is given as a block-and-replace strategy.

Discussion

Ketoconazole may also affect gonadal testosterone synthesis, resulting in decreased androgen levels and subsequent hypogonadism and gynecomastia in male patients; therefore, it is generally used as a second-line medical therapy in men. Metyrapone is FDA approved for the diagnosis of AI in the US and is used clinically, off label, for the treatment of CS. In the European Union, metyrapone is approved for the treatment of CS. Metyrapone exhibits potent, relatively selective inhibition of CYP11B1, but also inhibits the activity of CYP11B2. Significant reductions in urinary secretion of cortisol and aldosterone have been observed with metyrapone treatment. In a retrospective study of patients with CS who received metyrapone monotherapy, patients achieved control of cortisol levels. No escape was reported, and

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Received: 01-Nov-2022, Manuscript No. ACP-22-87032; **Editor assigned:** 04-Nov-2022, PreQC No. ACP-22-87032(PQ); **Reviewed:** 18-Nov-2022, QC No. ACP-22-87032; **Revised:** 23-Nov-2022, Manuscript No. ACP-22-87032 (R); **Published:** 30-Nov-2022; DOI: 10.4172/2472-0429.1000149

Citation: Tian H (2022) Oestrogen Conversion During cycle with External Testosterone. Adv Cancer Prev 6: 149.

patients treated for more than a year were controlled on a stable dose of metyrapone [3]. Metyrapone has been associated with gastrointestinal adverse events and hypoadrenalism. Despite the accumulation of adrenogenic and mineralocorticoid precursors associated with metyrapone treatment, incidence of metyrapone-related hirsutism, acne, and edema were rare, albeit not prospectively studied, and hypokalemia was reported but manageable with replacement. Of note, some patients were initially treated with anti-aldosterone drugs, which might have led to an underestimation of worsening of hypokalemia and hypertension. Although no clear recommendation has been made on this specific point, metyrapone is probably a better choice for a second-line medical treatment in females for whom a long-term treatment is necessary because of hyperandrogenism. Etomidate, an imidazole derivative, is used for the induction of anesthesia and is also a potent and dose-dependent inhibitor of CYP11B1, CYP17A1, and CYP11A1 [4]. Etomidate can be administered intravenously and is often used for seriously ill patients with severe hypercortisolemia who cannot take oral medication. However, only a few cases of its use have been reported in the literature.Earlier studies demonstrated that inhibition of cortisol was rapidly achieved with low-dose etomidate in patients with hypercortisolism and was distinct from the sedative effects of the drug. In patients with CS, etomidate treatment resulted in significant suppression of serum cortisol levels in infusion. In an emergency setting, patients with CS who received etomidate at a dose per hour exhibited rapid and prolonged suppression of serum cortisol levels. The most common side effects associated with etomidate were hypnotic effect, reduced blood pressure, myoclonus, dystonia, nausea, and vomiting. Adrenal insufficiency has also been reported, which may require glucocorticoid replacement, thus a block-and-replace protocol is used in most cases [5]. Etomidate is unstable in water, and is often administered in a formulation containing propylene glycol, which may increase the incidence of hemolysis and nephrotoxicity.Mitotane, a synthetic derivative of the pesticide ichlorodiphenyltrichloroethane, is indicated for the treatment of adrenocortical carcinoma, but in rare cases may be used for the treatment of hypercortisolemia. Mitotane inhibits CYP11A1, CYP11B1, CYP11B2, and 5α-reductase. In patients with CS, mitotane treatment has been associated with significant reductions in cortisol and androgen levels. In the largest study reported to date on the use of mitotane in CD, control of cortisol hypersecretion was observed in the patients after a median time of months; the mitotane level necessary to obtain control was lower than the level recommended for the treatment of adrenal carcinoma [6]. Interestingly, patients needed to be treated with hydrocortisone in parallel, probably due to adrenal atrophy, but this effect was transient in the majority of the patients, as withdrawal of the drug led to recurrence in them [7]. Results were similar in patients treated for ectopic ACTH secretion; patients achieved normal UFC levels after a mean time of several months. Mitotane is associated with a number of potential side effects, including hypercholesterolemia, anorexia, gastrointestinal symptoms, decreased memory and other neurological side effects, and abnormal liver function, these side effects lead to discontinuation of treatment in approximately a quarter of patients and require close monitoring of plasma mitotane levels [8]. A recent study of premenopausal women demonstrated a high incidence of menstrual disorders and ovarian macrocysts in women receiving mitotane, which may be related to elevated levels of luteinizing hormone, follicle-stimulating hormone, and estrogen as a consequence of mitotane alleviating the negative feedback normally exerted by the ovaries on the production of those hormones [9]. Osilodrostat is a potent and relatively selective inhibitor of CYP11B2 that also inhibits CYP11B1 at higher doses. In comparison to metyrapone, which also inhibits CYP11B1, osilodrostat is a more potent inhibitor of CYP11B1 and has a longer half-life. Osilodrostat was initially developed as a possible treatment option for hypertension, cardiac failure, and renal disease [10]. In studies in patients with hypertension, significant and dose-dependent decreases in urine and plasma levels of aldosterone and a blunting of the cortisol response to synthetic ACTH were observed. In a ten-week, proof-of-concept study in patients with CD who had previously undergone pituitary surgery and had UFC greater than the upper limit of normal, patients achieved normalization of UFC within weeks of initiating osilodrostat treatment, with all patients achieving decreases in UFC levels from baseline. After treatment discontinuation, UFC levels rose above the ULN. In a longer term, phase study of osilodrostat in patients with CD with UFC levels above the ULN, normalization of cortisol levels was achieved in patients by week and by the end of the study. In both studies, patients achieved normal UFC within a month of starting treatment.

Conclusion

Plasma levels of cortisol and aldosterone were decreased in both studies, while levels of their precursors, 11-deoxycortisol and 11-deoxycorticosterone, increased. Although blood pressure decreased from baseline in the proof-of-concept study, data from the phase 2 study showed no changes in blood pressure.

Acknowledgement

None

Conflict of Interest

None

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