Cushing's Syndrome: an update on current pharmacotherapy and future directions

Cortisol is an adrenal hormone essential for the maintenance of homeostasis, especially in response to stress. When cortisol levels are increased, this is defined as Cushing's syndrome (CS). CS can be associated with increased morbidity, and when untreated, increased mortality. Incidence varies from 0.7 to 2.4 per million population per year.

Cortisol production is stimulated by adrenocorticotropic hormone (ACTH), produced in the pituitary gland in the brain. Cortisol itself provides a negative feedback to this ACTH release. There are several causes of CS, i.e. 1) an ACTH producing pituitary adenoma (most frequently), 2) ectopic ACTH syndrome (EAS), or 3) primary adrenal disease, like an adrenal adenoma, - carcinoma, or - hyperplasia. Successful tumor-directed surgery is the keystone treatment modality for all causes of CS. Medical therapy for Cushing's syndrome is indicated when surgical treatment of the underlying cause is not successful or not feasible, and in case of acute complications of (severe) hypercortisolism. In the patients with severe and complicated CS, particularly in patients with EAS, rapid reversal of cortisol excess with medical therapy is needed. Pharmacotherapy in CS can have different targets, i.e. the corticotroph pituitary adenoma, suppression of steroidogenesis in the adrenal cortex, and blockade of cortisol action at tissue level by blocking the glucocorticoid receptor.

In the past four decades not much progress was made in the field of medical treatment of Cushing's syndrome (CS) until recent years. The adrenal blocking drugs metyrapone and mitotane were introduced in the sixties and early seventies respectively. In the eighties, the inhibitory effects on steroidogenesis of ketoconazole were identified as well as the usefulness of the glucocorticoid receptor antagonist mifepristone in selected cases. However, in that period no prospective trials have been performed with these drugs and no pituitary-directed drugs were available for patients with corticotroph adenomas. In the last decade, somatostatin and dopamine receptors have been identified as targets for medical treatment of pituitary-dependent CS and selected cases of ectopic ACTH production by neuroendocrine tumors. However, knowledge about long-term and extra-adrenal effects of medical therapy targeting aberrant receptors or their corresponding ligands needs to be expanded. Based on a randomized phase III trial, the universal somatostatin analog pasireotide was recently approved in Europe and the USA for treatment of pituitary-dependent CS. Combining pasireotide with the dopamine agonist cabergoline may have synergistic effects and this is currently investigated in a prospective multicenter trial. Future studies will also focus on tumor shrinking effects of these neuromodulatory drugs. Mifepristone was recently approved for treatment of CS with uncontrolled diabetes mellitus by the FDA, based on a prospective trial in patients with ACTH-dependent hypercortisolism. Prospective trials have now also been initiated with two 'new generation' steroid synthesis inhibitors, i.e. LCI699 and COR-003. Thus, the number of medical treatment options for CS has increased and this is important because in patients in whom surgery is unsuccessful or not feasible, the aim should be to completely normalize cortisol production.

Considering the relatively low complete remission rates with monotherapy, especially for patients with moderate-to-severe hypercortisolism, combination therapy is potentially more effective. This approach should be tailored according to patient- and drug characteristics. Future studies should be focused on the optimal order and combination of available drugs as well as the long-term efficacy and safety. Finally, future research should aim to identify new targets for medical treatment of the various forms of CS.

Sara Creemers
Department of Internal medicine, Division of Endocrinology,
Erasmus MC, Rotterdam, The Netherlands

Publication

Cushing's syndrome: an update on current pharmacotherapy and future directions.
Creemers SG, Hofland LJ, Lamberts SW, Feelders RA
Expert Opin Pharmacother. 2015