and PEGV make it attractive to use the two drugs in combination. Maybe it is time to challenge the existing concepts of treatment and monitoring of patients with acromegaly.

KEYWORDS: acromegaly, IGF-I, somatostatin, pegvisomant.

★ ★ ★

CUSHING'S SYNDROME: HOW TO SCREEN, DIAGNOSE AND TREAT TODAY WITH LINK TO THE FUTURE

R. Feelders

Erasmus University Medical Center, Rotterdam, Netherlands

Cushing's disease (CD), caused by a corticotroph pituitary adenoma, is associated with multi-system morbidity resulting in an impaired quality of life. When untreated or suboptimally treated, CD can lead to an increased mortality with cardiovascular disease as leading cause of death. Recently an etiological role for somatic mutations in ubiquitin specific peptidase 8 gene (USP8) has been identified in a subset of corticotroph adenomas. Inactivation of USP8 leads to increased epidermal growth factor receptor (EGFR) signaling and subsequently ACTH synthesis. EGFR may become a new therapeutic target in CD. Because of the gradual development of symptoms and the overlap in features of the metabolic syndrome, it can take years before the diagnosis CD is established. First-line screening tests are available to identify patients with CD, i.e. 24 h urinary free cortisol excretion, the overnight 1 mg dexamethasone suppression test and measurement of late night salivary cortisol levels (LNSC). LNSC can also be helpful to differentiate CD from conditions that are accompanied by activation of the pituitary-adrenal axis ('pseudo-Cushing states'), e.g. psychiatric disorders. Rarely, CD has a cyclical pattern which can hamper biochemical diagnosis. Preliminary data show that measurement of cortisol in scalp hair can reveal episodic cortisol overproduction in these patients. Transsphenoidal adenomectomy is the first choice of treatment for CD and remission rates vary between 60 and 90%. Treatment modalities for patients with persistent or recurrent disease include repeat surgery, radiotherapy, medical therapy and bilateral adrenalectomy. Medical therapy for CD can be classified into pituitary-directed drugs, adrenal-blocking drugs and glucocorticoid receptor antagonists. Dopamine and somatostatin receptors have been identified as targets for pituitary-directed drug therapy. The majority of ACTH-secreting pituitary adenomas expresses the dopamine receptor subtype 2 (DA2) and several studies show that the DA2 agonist cabergoline can normalize cortisol production in 25—40% of CD patients. Of the 5 known somatostatin receptor subtypes (sst), corticotroph pituitary adenomas predominantly express sst5, whereas sst2 expression is low due to down-regulating effects of high cortisol levels. Pasireotide is a universal somatostatin analog with high affinity for sst5 and the formulation for subcutaneous administration was recently approved for treatment of CD in Europe and the USA. A study with longacting pasireotide in CD is underway. Combined targeting of DA2 and sst5 with cabergoline and pasireotide showed promising results. Another potential therapeutic target includes cyclin-dependent kinases which were shown to be upregulated in corticotroph adenomas and which can promote cell growth via deregulation of the cell cycle. Metyrapone and ketoconazole are the most widely used adrenal blocking drugs. LCI699 and COR-003 are recently developed inhibitors of steroidogenesis and are currently under investigation in multicenter trials. Mifepristone is the only available glucocorticoid receptor antagonist and was recently approved in the USA for treatment of hyperglycemia related to CD. Importantly, morbidity of CD is not or only partially reversible in a substantial number of patients which is possibly related to the duration of pre-existing hypercortisolism. Therefore, after diagnosis cortisol production should be rapidly normalized with concomitant careful treatment of (cardiovascular) co-morbidity. Long-term follow-up is needed for CD patients to monitor complications of hypercortisolism and to detect recurrent disease.

KEYWORDS: cushing's syndrome, pituitary adenoma, ACTH, cortisol.

★ ★ ★

UPDATE ON THE MULTIDISCIPLINARY MANAGEMENT OF PITUITARY TUMOURS

M. Korbonits

Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

The pituitary gland is one of most fascinating organs of the body, as it has centrally important functions and also it is located in a unique anatomical position. It is the leader of the endocrine orchestra regulating multiple functions and it is sitting below the optic crossing and in-between the carotid arteries therefore no surprise that management of diseases of the pituitary requires an orchestra of expert colleagues itself. Starting with the diagnosis, we rely on family doctors, neurologists, rheumatologists, dermatologists, orthopaedic specialist, neurosurgeons, dentists, gynaecologists, cardiologists, ophthalmologists and optometrists but even jewellers (ring enlargements) and to make or at least suggest the diagnosis of acromegaly, Cushing's disease, prolactinoma, TSHoma, diabetes insipidus etc. While the diagnosis often is simple, in other cases numerous tests and discussions are needed to come to the right conclusions: skills of an interventional radiologists doing venous catheterisation or a vigilant biochemist testing for macroprolactin or the hook effect or special tests to solve the thyroid hormone resistance-TSHoma dilemma, helps out the endo-