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Making Education Easy

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Abbreviations used in this review:

AFTN = autonomously functioning thyroid nodules; **BMI** = body mass index; **CAD** = congenital adrenal hyperplasia; **DTC** = differentiated thyroid carcinoma; **GO** = Graves' orbitopathy; **TBII** = thyrotropin-binding inhibitory immunoglobulin; **TSI** = thyroid-stimulating immunoglobulin

Welcome to the Seventeenth edition of Endocrinology Research Review.

Highlights of this Review include, results of the DECISION trial, the first randomised, blinded, placebo-controlled trial of tyrosine kinase inhibitor therapy in advanced differentiated thyroid cancer to be published, which showed an improvement in progression-free survival with sorafenib vs placebo. We also report results of a pharmacokinetic analysis of a novel formulation of hydrocortisone designed to more closely mimic the normal diurnal variation of cortisol. And finally, we have included a prospective study of parathyroidectomy in non-diabetic haemodialysis patients with severe secondary hyperparathyroidism which finds a significant reduction in cardiovascular events with parathyroidectomy in this cohort.

We hope you find the selection for this month's edition useful in your practice, and we look forward to receiving your comments or feedback.

Kind Regards,

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Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial

Authors: Brose MS et al., on behalf of the DECISION investigators

Summary: This international multicentre, double-blind, placebo-controlled clinical trial randomised 417 patients with radioactive iodine-refractory locally advanced or metastatic differentiated thyroid cancer (DTC) to sorafenib or placebo. The primary endpoint was progression free survival (PFS). Placebo-treated subjects could crossover to active treatment upon progression. Sorafenib increased median PFS (10.8 months) vs placebo (5.8 months: HR 0.59; 95% CI 0.45-0.76; p<0.0001). Severity of adverse events associated with sorafenib was generally grade 1 or 2. The most frequently reported were hand-foot skin reaction (76.3%), diarrhoea (68.6%), alopecia (67.1%), rash/desquamation (50.2%).

Comment: This trial, known as DECISION, is the first randomised, blinded, placebo-controlled trial of tyrosine kinase inhibitor therapy in advanced DTC to be published. Participants had radioiodine non-avid or radioiodine-refractory disease that was mostly metastatic (96%) to lung (86%) rather than locally advanced (4%) and mostly FDG-PET positive (>75%). PFS improved from 5.8 to 10.8 months with sorafenib. Overall survival difference has not been ascertained, in part because of the cross-over design. CTC grade 3-4 adverse effects of sorafenib (hand-foot syndrome, diarrhoea, fatigue, weight loss, hypertension, and hypocalcaemia) were seen in 5-20% of those receiving sorafenib versus 0.5-2.4% on placebo. Results from the SELECT trial of lenvatinib in a similar group of DTC patients have just been presented at ASCO. These show a highly significant PFS advantage for lenvatinib of 18.3 months versus 3.6 months for placebo (HR 0.21). Thus we will then have two agents of proven value in advanced DTC as well as vandetanib and cabozantinib in advanced medullary thyroid carcinoma. Sorafenib and lenvatinib are both multikinase inhibitors with major VEGF-receptor inhibitor actions. Sorafenib now has a TGA indication for advanced DTC and a PBAC application is to be made. See also: Wells SA & Santoro M. Update: the status of clinical trials with kinase inhibitors in thyroid cancer. J Clin Endocrinol Metab 2014;99:1543-55

Reference: Lancet 24 April, 2014 [EPub ahead of print]

http://tinyurl.com/pz37ufx

^{131}I-MIBG therapy for malignant paraganglioma and phaeochromocytoma: systematic review and meta-analysis

Authors: van Hulsteijn LT et al.

Summary: The authors of this systematic review and meta-analysis aimed to investigate the effects of ^{131}I-MIBG on tumour volume in patients with malignant paraganglioma or phaeochromocytoma. The analysis included 17 studies and 243 patients who received treatment with ^{131}I-MIBG. Pooled proportions of responses were: complete response 0.03 (95% CI 0.06-0.15); partial response 0.27 (0.19-0.37); and stable disease 0.52 (0.41-0.62). Pooled proportions for hormonal response were: complete response 0.11 (0.05-0.22); partial response 0.40 (0.28-0.53); and stable disease 0.21 (0.10-0.40). Hormonal responses to ^{131}I-MIBG were better for patients with paraganglioma than phaeochromocytoma.

Comment: This is a systematic review of observational cohort studies. The apparent tumour responses by various methods, mostly WHO or RECIST criteria, were partial response (27%) and stable disease (52%). Similarly hormonal responses were mostly partial (40%) and stable (21%) catecholamine excess. Two studies reported PFS of 23.1 and 28.5 months, and another two studies had 5-year survivals of 45% and 64%. CTC grade 3-4 haematological toxicity was reported in 87% (neutropenia) and thrombocytopenia (83%). The regimens differed widely in dose and frequency of ^{131}I-MIBG and in selection criteria for therapy. Only one study used progressive disease as a criterion, thus stable disease may just be part of the natural history. There is no comparison with peptide receptor radionuclide therapy with ^{177}LuTate or ^{90}Y-lanreotide, multikinase inhibition with sunitinib or standard chemotherapy with cyclophosphamide, vincristine and dacarbazine (CVD), but toxicity does seem to be less than with CVD. Multicentre randomized trials with standardised criteria for treatment and assessment are needed.

Reference: Clin Endocrinol. 2014;80(4):487–501
http://tinyurl.com/k4zzf6y

Cardiovascular risk factors in children and adolescents with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

Authors: Subbarayan A et al.

Summary: The aim of this retrospective, cross-sectional study was to investigate the prevalence of cardiovascular risk factors in patients with congenital adrenal hyperplasia (CAH) with reference to recent changes in treatment regimens including lower steroid doses. Subjects were 107 children with a mean age of 9.2 years (range 0.4-20.5) with CAH due to P450c21 deficiency. Metrics were compared to UK growth reference data and the Fourth Task Force data set using standard deviation scores (SDS). Obesity was recorded in 23.6% (BMI SDS >2) and was significantly greater than in controls ($p<0.001$). Hypertension rates were 20.9% (systolic) and 8.8% (diastolic). Mean systolic, but not diastolic, blood pressure was greater than in the reference population ($p<0.001$ and $p=0.07$ respectively). Hyperlipidaemia occurred in 9.5% of subjects with CAH.

Comment: This is a report on CAH outcomes in children and adolescents from an expert centre. Oral hydrocortisone doses of 10-15 mg/m^2/day in 3-4 divided doses and fludrocortisone doses of 50-100 mcg/m^2/day were in accord with the Endocrine Society clinical practice guidelines. 17-hydroxyprogesterone morning levels and 24 hour means were still high, and over 60% had raised androstenedione levels. Almost 24% were obese, with weight SDS and BMI SDS above the population means, but this did not correlate with hydrocortisone dose. Almost 21% were hypertensive and 11% were pre-hypertensive, higher than in the reference population. The prevalence of obesity and hypertension were however lower than in a previous report from this centre in 2003 and this is ascribed to a reduced hydrocortisone dose, from a mean of 17.5 mg/m^2/day to 13.3 mg/m^2/day. Thus further improvements in therapy seem necessary. The authors speculate that sustained release hydrocortisone preparations or subcutaneous infusion pump therapy may provide this, but evidence is so far lacking and must await appropriately constructed trials.

Reference: Clin Endocrinol. 2014;80(4):471–7
http://onlinelibrary.wiley.com/doi/10.1111/cen.12265/abstract

Falsely undetectable TSH in a cohort of South Asian euthyroid patients

Authors: Drees JC et al.

Summary: Following identification of an index case in a woman of South Asian descent, a new phenomenon of functional TSH undetectable on 4 FDA-approved TSH immunoassays has been identified. The authors retested samples with TSH values <0.01 μIU/mL, and those with discordant results were subjected to retesting with up to 8 FDA-approved TSH immunoassays and TSHβ gene sequencing. 20 hypothyroid and euthyroid patients with shared ethnicity and falsely undetectable TSH in 4/8 assays were identified from a sample of around 2 million. Chart review revealed all had fT4 and fT3 values inconsistent with the undetectable TSH results. The authors have identified a novel TSHβ mutation in these subjects, and pinpointed specific antibodies in the 4 assays which fail to bind to these variants.

Comment: This is a very detailed report of the processes leading to the identification and the investigation of discordant, artefactual, very low TSH results, which proved to be due to a homozygous single nucleotide mutation causing a single amino acid change resulting in the failure of binding of the monoclonal antibody used in four widely used TSH assays and thus absence of assay signal. This abnormality is rare, perhaps 0.001-0.006% of the studied population, but likely higher in populations enriched in Asian ethnicity (Indian, Pakistani, Chinese). Despite none of these patients having raised fT4 or fT3, inappropriate anti-thyroid drug treatment or reduction in thyroxine dose was initiated in almost half. The obvious importance of interpreting a TSH with fT4 and fT3 to secure a biochemical diagnosis of hyperthyroidism, and of making a clinical diagnosis, is thus emphasised, and also the value of enlisting the clinical biochemist in further evaluation when the results are unusual or not in accord with clinical assessment.

Reference: J Clin Endocrinol Metab. 2014;99(4):1171-9
http://tinyurl.com/k3z2mr6

An oral multiparticulate, modified-release, hydrocortisone replacement therapy that provides physiological cortisol exposure

Authors: Whitaker MJ et al.

Summary: This report details development of a novel hydrocortisone replacement therapy (DIURF-006) which mimics physiological cortisol exposure using an enteric, delayed release system. Pharmacokinetic analyses were conducted in 16 dexamethasone-suppressed human volunteers who received a twice-daily 'toothbrush' dosing regimen, comprising 20 mg DIURF-006 at 11 pm and 10 mg at 7 am, and demonstrated that cortisol levels with DIURF-006 were similar to physiological profiles. There was a linear relationship between cortisol levels and DIURF-006 doses between 5 and 30 mg. Bioavailability of DIURF-006 was 89% vs hydrocortisone.

Comment: This study reports pharmacokinetic analysis in dogs and humans of a novel formulation of hydrocortisone designed to more closely mimic the normal diurnal variation of cortisol, Chronocort®. Plenadren® is a formulation licensed in the EU, with an immediate release coating and a sustained release core but it has 20% less bioavailability than standard immediate release hydrocortisone and an equivalent C_{max}. In contrast, Chronocort® is a multiparticulate formulation with an inert microcrystalline core coated with a drug layer then a polymer layer to modify drug release. Various compositions were tested and one, designated DIURF-006, taken forward into detailed assessment. When taken in a 'reverse' dosing of 20 mg at 2300h and 10 mg at 0700h DIURF-006 produces a physiological C_{max}, T_{max}, and AUC, and serum cortisol is dose-proportionate. This formulation is clearly worthy of clinical assessment in CAH and Addison's disease to see if the more physiological pharmacokinetics has clinical benefit. As developmental and production costs are likely to be much higher than standard hydrocortisone preparations, proof of clinical benefit will be essential to obtain cost subsidy e.g. support from the PBAC.

Reference: Clin Endocrinol. 2014;80 (4):554–61
http://onlinelibrary.wiley.com/doi/10.1111/cen.12316/abstract

Clinical characteristics of Graves' orbitopathy in patients showing discrepancy between levels from TBII assays and TSI bioassay

Authors: Jang SY et al.

Summary: The investigators in this comparative case series assessed endocrine and ophthalmic clinical characteristics in 317 subjects with Graves' orbitopathy (GO) and discrepancies between thyroid-stimulating immunoglobulin (TSI) and thyrotropin-binding inhibitory immunoglobulin (TBII) levels.

Comment: This is an interesting contribution to the difficult question of factors influencing Graves' ophthalmopathy/orbitopathy (GO, or thyroid-associated eye disease), although the explanation for the findings is unclear. In general we interpret assays for TSI and TBII as measuring the same thing i.e. stimulation, although we recognize that a blocking antibody will give a signal in a TBII assay. In this study the TSI assay used CHO cells with a transfected chimeric human-rat TSH receptor and a luciferase reporter, and the TBII assay used a labeled monoclonal TSH-receptor antibody to compete for TSH receptor binding. The clinical eye manifestations in Korean patients with discordant TSI and TBII assays were examined and indicated that where TSI was above the mean and TBII below, the clinical activity score (CAS) for GO and the NOSPECS score for severity were both higher than when TBII was above the mean and TSI below, with more prevalent lid retraction, soft tissue, extra-ocular muscle, and optic nerve involvement. Paradoxically in this patient group there were more patients with active hyperthyroidism when TBII was above the mean and TSI lower. The authors reference data that TBII has a stronger association with hyperthyroidism in Asians than in Europids. Nevertheless TSI is associated with GO manifestations in Asians. Despite this discrepancy the overall correlation of both TSI and TBII with hyperthyroidism in this study was strong. Presumably the two assays may detect subtle differences in receptor binding characteristics influencing thyroid stimulation and orbital fat/muscle differently. The pathogenesis of GO continues to be subtle and elusive.

Reference: Clin Endocrinol. 2014;80(4):591–7
http://onlinelibrary.wiley.com/doi/10.1111/cen.12318/abstract

Parathyroidectomy improves cardiovascular outcome in nondiabetic dialysis patients with secondary hyperparathyroidism

Authors: Lin H-C et al.

Summary: The authors of this cohort study aimed to examine associations between parathyroidectomy (PTx) and major cardiovascular events. Subjects were 53 non-diabetic dialysis patients with severe, secondary hyperparathyroidism and intact parathyroid hormone levels who were receiving maintenance haemodialysis. Medical treatment alone was received by 23 patients, whilst 30 received medical treatment plus PTx. Both groups had similar baseline characteristics. Mean follow-up was 72 months. Subjects in the PTx group had a lower risk of cardiovascular events (p=0.021), and significant improvements in other parameters including blood pressure, haemoglobin, alkaline phosphatase (ALP), calcium, phosphate and calcium phosphate product. Treatment modality (medical therapy vs PTx) was the only variable associated with major cardiovascular events on multiple Cox regression analysis: HR 26.12 (95% CI 1.30-562.27, p=0.033).

Comment: This was a prospective study of parathyroidectomy in severe hyperparathyroidism of renal failure on haemodialysis, in the worst 7.7% of the study centre's patients. The subsequent difference in the rate of the cardiovascular events of stroke, acute MI, and death were strongly in favour of PTx with medical therapy vs medical therapy alone. This was not a randomised controlled trial as the control group were those who refused PTx. Those who received PTx had higher serum calcium, higher calcium phosphate product and higher Charlton co-morbidity index but these differences would have tended to mitigate any benefit of PTx. PTx achieved lower systolic and diastolic blood pressures, reduced calcium, phosphate and ALP. The mechanism of the benefit is unclear but may be reduced vascular calcification, and reduced vascular smooth muscle collagen production, both reducing vascular stiffness. Overall the reduction of cardiovascular events in this study provides hard endpoint data to support PTx in severe secondary hyperparathyroidism in non-diabetic patients on haemodialysis.

Reference: Clin Endocrinol. 2014;80(4):508–15
http://onlinelibrary.wiley.com/doi/10.1111/cen.12333/abstract

Differentiating between Cushing's disease and pseudo-Cushing's syndrome: comparison of four tests

Authors: Alwani RA et al.

Summary: This prospective study reports the diagnostic performance of 4 testing methods to distinguish Cushing's disease (CD) from pseudo-Cushing's disease (PCS): the circadian rhythm of serum cortisol levels; midnight serum cortisol (mserC); late-night salivary cortisol (LNSC) concentration; and the dexamethasone-CRH (Dex-CRH) test. The 73 subjects had clinical features of hypercortisolism, plus insufficient suppression of serum cortisol following 1 mg dexamethasone, ± elevated cortisol excretion in 24-hour urine samples. The positive predictive value (PPV) for CD for cortisol midnight:morning ratio >0.67 was 100% (negative predictive value [NPV] 73%). PPV for MserC >243 nmol/L was 98% (NPV 95%); LNSC >9.3 nmol/L had a PPV of 94% (NPV 100%). There was a PPV of 100% (NPV 90%) for Dex-CRH following 2 days of dexamethasone suppression and a CRH-stimulated cortisol level >87 nmol/L (T = 15 min).

Comment: The diagnosis of mild Cushing's syndrome especially Cushing's disease (CD) is one of the most difficult clinically and hormonally in endocrinology. The distinction of CD from pseudo-Cushing's syndrome (PCS) is especially challenging, given that patients with true CD may have associated conditions also associated with PSC such as physical stress, psychological stress, and depression. The original report of Yanovski et al. (JAMA 1993;269:2234) of the high accuracy of a combined dexamethasone suppression and CRH stimulation test (Dex-CRH) to distinguish between the two conditions was not replicated by others (Erickson et al. J Clin Endocrinol Metab. 2007;92:2972 ; Martin et al. J Clin Endocrinol Metab. 2006;91:2582; and Pecori Giraldi et al. Clin Endocrinol. 2007;66:251). This is a report of a prospective evaluation of 73 patients in whom the final diagnosis was CD in 53 (surgically-validated) and PSC in 20 (either resolved with treatment of cause, or did not progress). The midnight-to-morning serum cortisol ratio was helpful, as was the midnight serum cortisol or late night salivary cortisol i.e. higher late night cortisol in CD versus PCS. The DEX-CRH test was highly predictive of CD if the serum cortisol was >87 nmol/L, 15 minutes after CRH. While additional data are welcome, reliance on specific cut-off values may be unwise and diagnosis must utilise multiple clinical and laboratory assessments, including observation over time if possible.

Reference: Eur J Endocrinol. 2014;170:477-86
http://www.eje-online.org/content/170/4/477.abstract

MicroRNA profile of poorly differentiated thyroid carcinomas: new diagnostic and prognostic insights

Authors: Dettmer MS et al.

Summary: This study aimed to characterise microRNA (miRNA) expression profiles in conventional poorly differentiated (PD) and oncocytic poorly differentiated (oPD) thyroid carcinomas; compare them with profiles of well-differentiated thyroid tumours; and identify diagnostic and prognostic markers. miRNA expression (n=768 miRNAs) was studied using PCR-microarrays for specimens from normal thyroid (n=8); PD (n=14), oPD (n=13) and well-differentiated thyroid carcinomas (n=72).

Comment: MicroRNAs are small non-coding RNA molecules of about 22 nucleotide lengths which can regulate transcriptional and post-transcriptional gene expression by silencing of complementary mRNA sequences. This is the first comprehensive miRNA profile for poorly differentiated thyroid carcinomas of PD and oPD (Hurthle) type in the literature. PD and oPD are biologically situated between well-differentiated papillary and follicular thyroid carcinomas (PTC and FTC) on the one hand, and anaplastic thyroid carcinomas (ATC) on the other. These neoplasms are known to be particularly difficult to diagnose. PDs can be admixed with well-differentiated thyroid tumours such as PTCs or FTCs, but even a small PD component determines the patient outcome. There is an even worse outcome for oPD compared with conventional PD. This study shows that several miRNAs may be used diagnostically to distinguish between PTC/FTC and PD. A subset of the significantly deregulated miRNAs has an impact on patient survival and can predict tumour relapse and survival even in tumours with such an adverse outcome. These miRNAs are known to play important roles in other malignancies, such as oesophageal squamous cell carcinoma for miR-150 or prostate cancer for miR-23b. This sort of detailed genetic analysis will progressively guide decision-making in therapy and follow-up of thyroid cancer.

Reference: J Molec Endocrinol. 2014;52(2):181-9
http://jme.endocrinology-journals.org/content/52/2/181.abstract

TSH measurement is not an appropriate screening test for autonomous functioning thyroid nodules: a retrospective study of 368 patients

Authors: Chami R et al.

Summary: The authors of this retrospective study reviewed thyroid scans in 217 patients with solitary autonomously functioning thyroid nodules (AFTN), no other thyroid nodules > 10mm and a lack of co-morbidities affecting thyroid function, in order to determine associations between serum TSH and AFTN. Patients diagnosed with AFTN had normal serum TSH in 49% of cases

Comment: Current guidelines for evaluation of thyroid nodules do not suggest a radionuclide thyroid scan if serum TSH is normal, but this retrospective study of AFTN finds virtually half are not associated with low serum TSH. Although an association of bigger nodule size with lower TSH was found, TSH could be normal in nodules up to 10 mL volume or 4 cm diameter, and hyperthyroidism could occur in 2 cm diameter nodules. The authors' definition of an AFTN was an increase in uptake compared to extranodular thyroid tissue, rather than with a degree of uptake suppression in the extranodular thyroid tissue, which would clearly influence the prevalence of low TSH. The authors suggest that routine use of radionuclide scan to identify AFTN enables avoidance of fine needle biopsy. It is unclear that the negligible risk of malignancy in a hot nodule with suppression of uptake in the rest of the gland applies to euthyroid AFTN.

Reference: Eur J Endocrinol 2014;170:593-9
http://eje-online.org/content/170/4/593.abstract

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