Indian Journal of Clinical Practice, Vol. 29, No. 11, April 2019

ESICON 2018: 48th Annual Conference of Endocrine Society of India

NOVEMBER 15-18 | MAYFAIR CONVENTION, BHUBANESWAR

EVOLVING LANDSCAPE OF DPP-4i CVOTs WITH CARMELINA IN FOCUS

Dr Sanjay Kalra, Haryana

- Linagliptin is a single-dose dipeptidyl peptidase-4 inhibitors (DPP-4i) with established clinical efficacy and safety. It is the only globally available DPP-4i excreted mainly via gut/bile. The drug requires no dose adjustment.
- The CARMELINA trial was designed to evaluate the cardiovascular (CV) and kidney safety of linagliptin in patients with type 2 diabetes mellitus (T2DM) vs. placebo. Primary endpoints included CV death, nonfatal myocardial infarction (MI) and nonfatal stroke. Key secondary endpoint included sustained estimated glomerular filtration rate (eGFR) decrease by ≥40%, progression to sustained end-stage kidney disease (ESKD) and death due to kidney disease. Patients included in the trial had established cardiovascular disease (CVD), kidney disease or both. Patients with T2DM were randomized to oral treatment with linagliptin or placebo on top of standard of care.
- The trial included a broad group of kidney disease patients.
- The trial showed no increased risk for hospitalization for heart failure (HF) even in high-risk patients with pre-existing HF.
- Event rate of hospitalized HF was 2.8 times higher in patients with eGFR <45.
- The long-term kidney safety profile of linagliptin was confirmed in the first prespecified adjudicated kidney outcome data with DPP-4i.
- The number of patients who had ≥1 new glucose-lowering medication introduced post-baseline was significantly lower with linagliptin compared to placebo.
- With linagliptin, fewer patients initiated or increased insulin dose.
- Overall, linagliptin did not increase the risk of hypoglycemia.
- The trial showed a reassuring long-term kidney safety profile. It fills a data gap as it included patients across the full range of kidney function.
- With CARMELINA, linagliptin showed a reassuring CV safety profile and a robust and reassuring HF safety.

DIABETIC KIDNEY DISEASE AND ROLE OF SGLT-2i

Dr Mathew John, Trivandrum

- Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) act by inhibiting SGLT-2 in the proximal tubule of the kidney, thereby increasing natriuresis and glucose excretion.
- They have beneficial effects on weight, systolic BP and glycated hemoglobin (HbA1c).
- Large cardiovascular outcomes trials (CVOTs) have found reductions in composite major adverse cardiac events (MACE), HF hospitalization, CV death and various composites of CV outcomes.
- Most of the data regarding the long-term effects on the kidney are derived from the CVOTs: EMPA REG OUTCOME, CANVAS and DECLARE TIMI.
- About 70-90% of subjects enrolled in CVOTs of SGLT-2i did not have diabetic kidney disease (DKD).
- Mechanisms of renal protection with SGLT-2 blockers - Restoring tubuloglomerular feedback; reducing renal hypoxia; changes in renal substrate utilization; improvements in BP; improvements in glycemia; improvements in weight and reducing uric acid levels.
- Key benefits of SGLT-2i in DKD - Retard the progression of eGFR in subjects with proteinuric DKD; retard the progression of microalbuminuria to macroalbuminuria; retard the progression of macroalbuminuria to ESRD; reduce the risk of new-onset albuminuria; reduce various CV outcomes in subjects with DKD.

MANAGEMENT OF NEUROENDOCRINE TUMORS

Dr Karel Pacak, USA

- Classification of neuroendocrine tumors (NETs) - Carcinoids and gastroenteropancreatic tumors (GEPs); Chromaffin cell tumors; Multiple endocrine neoplasia (MEN)1-, MEN2-, neurofibromatosis (NF)1-related NETs; Medullary thyroid carcinoma (MTC); Poorly differentiated small cell carcinoma; NETs of unknown origin.
- Early accurate diagnosis leads to better prognosis.
- NETs - Specific characteristics: Take up hormone precursors; Synthesize, store and release hormones; Express specific transporters and receptors; Have specific metabolomic profiles; They are immunogenically cold.
- Endoscopic methods in NETs negative on imaging - Capsule endoscopy; Double balloon enteroscopy.
- The North American Neuroendocrine Tumor Society (NANETS) recommendation for NETs - *Surgery*: 50% recurrence rate; surveillance should continue beyond 5 years, not clear if 10 years but recommended, especially for young patients and those with positive LNs. *Surveillance*: Every 6-12 months, CT/MRI abdomen, initially Octreoscan or ^{68}Ga-DOTATATE recommended.
- A study evaluated the efficacy and safety of lutetium-177 (^{177}Lu)-DOTATATE in patients with advanced, progressive, somatostatin-receptor-positive midgut NETs. The treatment led to markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide long-acting repeatable (LAR) (Strosberg J, et al. *N Engl J Med.* 2017;376(2):125-35).

DIGITAL DIABETOLOGY: DAILY PRACTICALITIES

Dr AG Unnikrishnan, Pune

- Trust your patient, but do not let that stop you from verifying records if a discrepancy is noted.
- Rule out other causes of false rise in HbA1c.
- Consider the possibility of malfunctioning glucometer.
- Calibrate or change the device. In our setting, make sure that the glucometer is used by a single person.

IN-HOSPITAL MANAGEMENT OF DIABETES MELLITUS

Dr Arpan Dev Bhattacharyya, Bengaluru

- Diabetes control in hospital is important.
- The target needs to be clear.
- Insulin is certainly the agent of choice.
- TEAM approach is the KEY to success.
- Regular audit of our own work helps to improve the quality of care we provide.
- Glycemic targets that can be recommended in different patient populations - Not recommended: <110 and >180 mg/dL; May be appropriate: 110-140 mg/dL and Recommended: 140-180 mg/dL.
- Criteria of good control - Good: 80% or more; Suboptimal: 40-80% and Poor: <40% (in the target range).
- A survey at the Manipal Hospital suggested that increased attention needs to be paid to improving glycemic control in patients hospitalized for reasons other than diabetes. Using subcutaneous insulin, glycemic control was good in 48%, suboptimal in 15% and poor in 37% of patients. The corresponding numbers while on intravenous insulin were 45%, 11% and 46%, respectively (Deepak PJ, et al. *Postgrad Med J*. 2003;79(936):585-7).

ENDOCRINE MANAGEMENT OF GENDER INCONGRUENT PERSON

Dr Mala Dharmalingam, Bengaluru

- Individuals should be treated with the lowest effective hormone doses, and the focus of treatment should be based on the individual's response and not just hormone levels.
- Patient safety is of utmost concern.
- Side effects should be monitored.

DIAGNOSIS AND MANAGEMENT OF MENOPAUSE

Dr Ganapathi Bantwal, Bengaluru

- Hormone therapy (HT) is the most effective treatment for vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM).
- The concept of "lowest dose for the shortest period of time" may be inadequate or even harmful for some women.
- A more fitting concept is "appropriate dose, duration, regimen and route of administration."
- Decision on duration requires individualization.
- Given the more favorable safety profile of estrogen alone, longer durations may be more appropriate.
- Risk stratification by age and time since menopause is recommended (<10 years from menopause or <60 years).

- Transdermal or lower doses of HT may decrease risk of VTE and stroke.
- Micronized progesterone is a safer alternative when use of progesterone is considered.

HEART FAILURE - AN ELEPHANT IN THE ROOM: MANAGEMENT IN THE ERA OF SGLT-2i

Dr Sundar Mudaliar, California

- Cardiovascular disease is more than MACE (MI, CVA, CV death).
- HF is an important component of CVD.
- HF is quite prevalent in patients with diabetes; occurs in >1 in 5 patients aged over 65 years.
- Patients with both diabetes and HF have a poor prognosis, with a median survival of ~4 years.
- Diabetes can lead to HF through both atherosclerotic-mediated and atherosclerotic-independent mechanisms.
- In a network meta-analysis, the use of SGLT-2i or glucagon-like peptide (GLP)-1 was associated with lower mortality in patients with T2DM.
- SGLT-2i have moderate benefits on atherosclerotic MACE in patients with established atherosclerotic cardiovascular disease (ASCVD). Additionally, they have robust benefits on reducing hospitalization for HF and progression of renal disease regardless of existing ASCVD or a history of HF.

ADA-EASD 2018 CONSENSUS: IN INDIAN CONTEXT

Dr Awadhesh K Singh, Kolkata

- Sulfonylureas (SUs) and thiazolidinediones (TZDs) remain the cornerstone of therapy in a developing country where the patient has to pay from his pocket.
- Alpha-glucosidase inhibitors (AGIs) are not included in ADA-EASD consensus as they are not used in the USA, but are still useful in Indians.
- GLP-1 receptor agonists (GLP-1RAs) and SGLT-2i should be used in established CVD, given the data we have.
- SGLT-2i have data suggestive of prevention of hospitalization for HF in T2DM and thus should be used if patients can afford.

ADRENAL INSUFFICIENCY IN CHILDREN

Dr David Torpy, Australia

- Adrenal insufficiency refers to low plasma cortisol, often confirmed by adrenocorticotropic hormone (ACTH) stimulation testing.
- Majority of adrenal insufficiency cases in children (primary/secondary) have a genetic etiology. Testing is based on AI category and associated features. Precise diagnosis may assist in prognosis/management and may assist with family counseling/prenatal diagnosis.
- Adrenal crisis is an acute deterioration in health associated with hypotension. Resolution occurs following parenteral glucocorticoid administration.
- Adrenal insufficiency treatment in children (chronic) - Treatment with hydrocortisone in 2 or 3 divided doses (total daily dose 8-12 mg/m^2 body surface area [BSA], 0.2-0.3 mg/kg) over other types of glucocorticoids replacement therapies; In children with primary adrenal insufficiency, synthetic, long-acting glucocorticoids should be avoided; In confirmed aldosterone deficiency, fludrocortisone can be given; In infants, sodium chloride supplements should be given.
- Adrenal crisis treatment in children - Hydrocortisone IV doses (<3 years - 25 mg; 3-12 years - 50 mg; >12 years - 100 mg; OR Hydrocortisone 100 mg/m^2 BSA); Bolus D5 normal saline 20 mL/kg over 1 hour, further infusion based on standard resuscitation guidelines.
- Adrenal insufficiency in children is rare. Suspect if there is fatigue, weight loss, upper gastrointestinal distress, hypotension, especially if chronic or subacute.
- Clinical assessment of BP, especially for postural hypotension is useful.
- Hypoglycemia, and hyponatremia are common; hyperkalemia and pigmentation are not reliably present.
- Around 50% have congenital adrenal hyperplasia (CAH), 30% autoimmune, adrenal insults, ACTH resistance and other genetic causes follow. Associated features are key to establishing genetic cause.
- Adrenal insufficiency challenges - Glucocorticoid dosing: There is no reliable biochemical marker of tissue glucocorticoid sufficiency; Adrenal crises are frequent (6-8%/year) and the current preventive strategies not fully effective; Impaired well-being in 40% treated adults (?children).

COMBINATION OF EMPA AND LINA: A LEAP TOWARDS HOLISTIC DIABETES MANAGEMENT

Dr Sujoy Majumdar, Kolkata

- Empagliflozin/linagliptin fixed-dose combination (FDC) offers high efficacy with convenience of a single tablet, thereby reducing the pill burden.

- There are 2-4 times higher odds of patients reaching the goal HbA1c compared to individual agents. It is associated with early achievement of glycemic goal with durable efficacy.
- The combination offers extraglycemic benefits like weight reduction, BP control, overall CV and renal safety, etc.
- There is absence of any additional safety concerns, or drug interactions.
- To summarize, Empa/Lina combination till date remains one of the best steps towards holistic management of diabetes mellitus.

TENELIGLIPTIN: RECENT EVIDENCES

Dr Sujoy Ghosh, Kolkata

- Teneligliptin is a specific DPP-4i with dual excretion through hepatic and renal routes.
- No dose adjustment is required in hepatic (mild and moderate) or renal plasma dysfunction. It can be administered irrespective of meals.
- Once a day dosing is possible and the drug has low potential for drug-drug interactions.
- Treatment with teneligliptin results in significant reduction in HbA1c, fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). It is weight neutral and has low risk of hypoglycemia.
- The drug is generally well-tolerated.
- Teneligliptin has been found not to cause detectable increase in CV risk in Japanese and Indian studies. The drug had no clear effect on the occurrence of CV adverse events, vital signs, ECG or lipid parameters.

MAKING CHOICES: DPP-4i, SGLT-2i OR BOTH IN TAKING NEXT STEP AFTER METFORMIN

Dr JJ Mukherjee, Kolkata

- Combination of DPP-4i and SGLT-2i results in greater improvement in glycemic control than each individual component alone.
- SGLT-2i/DPP-4i vs. DPP-4i alone yields greater reductions in HbA1c and FPG.
- SGLT-2i/DPP-4i vs. SGLT-2i alone - additional reductions in HbA1c and FPG are less marked.
- HbA1c reduction due to SGLT-2i/DPP-4i combination vs. DPP-4i alone seems to be directly proportional to baseline HbA1c.
- In contrast, additional HbA1c reduction due to SGLT-2i/DPP-4i combination vs. SGLT-2i alone seems modest regardless of baseline HbA1c.
- While the combination of SGLT-2i and DPP-4i results in a clinically meaningful reduction in HbA1c and FPG with low risk of hypoglycemia, the additional glucose control is significant when SGLT-2i is combined with or added to DPP-4i, but not the other way round.
- Action of SGLT-2i is unlikely to be affected by combined use with DPP-4i.

INHALED CORTICOSTEROIDS AND HPA AXIS SUPPRESSION: HOW IMPORTANT IS IT AND HOW SHOULD IT BE MANAGED?

Dr Kalpana Dash, Raipur

Corticosteroids are very important in treating bronchoconstrictive lung disorders. However, inhaled corticosteroid (ICS) preparations play a central role in treating chronic obstructive pulmonary disease (COPD) and asthma, limiting the exposure to systemic steroid therapy and its long-term consequences.

More potent ICS therapy has significant absorption across the lungs, leading to hypothalamic-pituitary-adrenal (HPA) axis suppression, iatrogenic Cushing's syndrome, adrenal insufficiency, very rarely osteoporosis, growth failure in children and development of posterior subcapsular cataract. This is much higher in 'higher risk' patients exposed to high cumulative ICS doses, and in those treated with frequent oral corticosteroids or drugs which inhibit cytochrome P450 3A4, like ritonavir and antidepressant drugs.

There are different ICS available like beclomethasone dipropionate (BDP), budesonide, ciclesonide, fluticasone propionate and mometasone furoate.

They all have common mode of action by binding to glucocorticoid receptors. Early detection of adrenal suppression after ICS therapy is required and biochemical testing needs to be done to confirm the diagnosis, and careful patient education about the need for steroid supplementation at times of stress is an important part of management.

DIAGNOSIS AND MANAGEMENT OF MALE HYPOGONADISM

Prof Subhankar Chowdhury, Kolkata

- Diagnosis of male hypogonadism is made by testing early morning fasting testosterone by reliable assay in appropriate clinical setting.
- Treatment options depend on etiology (primary/secondary); fertility concern; age of patient and safety issues.

- It is important to treat the primary/underlying cause.
- Primary hypogonadism requires testosterone therapy. Fertility options include TESE and ICSI, donor sperm and adoption.
- In secondary hypogonadism, gonadotropin therapy improves fertility.
- Testosterone therapy monitoring - Target testosterone: Mid-normal range for healthy young males; Serum testosterone and packed cell volume (PCV): 3-6 months post-initiation, then yearly; PCV >54% - stop therapy, till it decreases to <50%, evaluate for hypoxia and sleep apnea and reinitiate with a reduced dose; PSA: 3-12 months post-initiation if age >40 years. Δ PSA >1.4 ng/mL or absolute value >4 ng/mL warrants urology referral.
- Pubertal induction in boys with isolated hypogonadotropic hypogonadism (IHH) - Injection testosterone monthly; start with low-dose, with 6-monthly increments; Reach adult dose over 3-4 years; Adult dose - 200 mg/2 weekly or 100 mg/week.
- Testosterone replacement in hypogonadal males: Benefits >>> risks.

MANAGEMENT OF GRAVES' ORBITOPATHY: AN UPDATE

Dr Wilmar M Wiersinga, Netherlands

- In a study conducted to construct a predictive score for the development or progression of Graves' orbitopathy (GO) in Graves' hyperthyroidism (GH), among patients without GO at diagnosis, 15% developed GO (13% mild, 2% moderate-to-severe) during subsequent treatment with ATD. Independent baseline determinants for the development of GO included clinical activity score, thyroid-stimulating hormone (TSH)-binding inhibitory immunoglobulins, duration of hyperthyroid symptoms and smoking.
- A recent study compared the efficacy and safety of add-on mycophenolate to methylprednisolone in comparison with methylprednisolone alone in patients with moderate-to-severe GO. While there were no significant differences in the rate of response at 12 weeks or rate of relapse at 24 and 36 weeks, post-hoc analysis suggested that addition of mycophenolate improved rate of response to therapy by 24 weeks in patients with active and moderate-to-severe GO (Kahaly et al. *Lancet Diab Endocrinol.* 2018;6(4):287-98).
- Selenium is known to improve mild GO and prevents deterioration of mild GO. Promising new therapies in active moderate-to-severe GO include rituximab, teprotumumab and tocilizumab. But, IV steroids remain the treatment of choice until RCTs comparing steroids with these novel agents show greater efficacy and better tolerability. It is too early to dismiss rituximab as a disease-modifying drug and too early to accept it as an alternative to IV methylprednisolone. Therefore, rituximab currently has a role in resistant cases, not responding to steroids.

EVOLVING GLIPTIN – EVOGLIPTIN

Dr Awadhesh K Singh, Kolkata

- Evogliptin (DA-1229) is a piperazine derivative. It is a selective, potent and reversible inhibitor of DPP-4.
- The agent has been studied in a Phase II study and two Phase III studies in South Korea in T2DM patients.
- According to a recent study, evogliptin 5 mg monotherapy significantly decreased HbA1c and was well-tolerated in patients with T2DM inadequately controlled on diet and exercise.
- The results suggested that T2DM patients with modest hyperglycemia may be good candidates for evogliptin monotherapy.
- Evogliptin 5 mg added to metformin therapy has been found to improve glycemic control and was non-inferior to sitagliptin and well-tolerated in T2DM patients inadequately controlled by metformin alone. Evogliptin is a weight-neutral agent and has minimal potential for drug interactions. It can be used safely in patients with renal dysfunction.

THYROID MICROCARCINOMAS – TO TREAT OR NOT

Dr Bipin Kumar Sethi, Hyderabad

Increasing surveillance has led to detection of many thyroid nodules that the patients would have lived (and died) happily with. Detection of a nodule should not lead to further work-up (FNAC) unless otherwise indicated. All lesions without the high risk characteristics can be offered the choice of observation, and if they are operated, could have the choice of less extensive surgeries. Active follow-up is the key to the plan of surveillance should the patient choose this path. Active surveillance does not mean no treatment. Treatment is delayed until the cancer shows significant progression.

Your Trust
Matters the Most
for Our
Teneligliptin

In Type 2 Diabetes...

Rx

GLYPTEN

Teneligliptin 20 mg

Trust... Transition... Teneligliptin

DIABÉTIX
A Division of
FRANCO-INDIAN
PHARMACEUTICALS PVT. LTD.

2019