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BLUGLIP (VILDAGLIPTIN) GIVES BETTER TIME IN RANGE AND LESS GLYCEMIC VARIABILITY COMPARED TO OTHER DIPEPTIDYL PEPTIDASE-4 INHIBITORS

A strong correlation exists between type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), which is the leading cause of morbidity and mortality in patients with diabetes.

Time-in-Range (TIR), a newly developed metric for evaluating glycemic management, is rapidly being linked to outcomes associated with diabetes.

TIR, is the amount of time those with diabetes spend with their blood glucose levels in a recommended target range and is represented as a percentage. Thus, the range is the amount of time spent in the target blood glucose range-between 70 and 180 mg/dL. A TIR above 70% is recommended which is about 17 hours of a 24-hour day.

The usefulness of TIR as a surrogate marker of long-term negative clinical outcomes is supported by the known connection between lower TIR and an increased risk of all-cause and CVD death among patients with type 2 diabetes mellitus (T2DM).

There is growing evidence supporting the association between TIR, and diabetes-related outcomes. A large prospective cohort study has found that TIR as measured by continuous glucose monitoring (CGM) during hospitalization was found to be inversely linked with long-term risks of all-cause and CVD mortality in patients with T2DM. These findings back up the efficacy of TIR as a predictive marker for long-term adverse clinical outcomes. In both type 1 and type 2 diabetes, TIR has been linked to microvascular complications as diabetic retinopathy, micro albuminuria, nephropathy, and neuropathy.

Treatment of T2DM and CVD differs widely across and within countries, and although most of the CVD risk in T2DM can be attributed to the long-term complications of diabetes, interest has been growing in studying the effect of antidiabetic drugs on this risk.

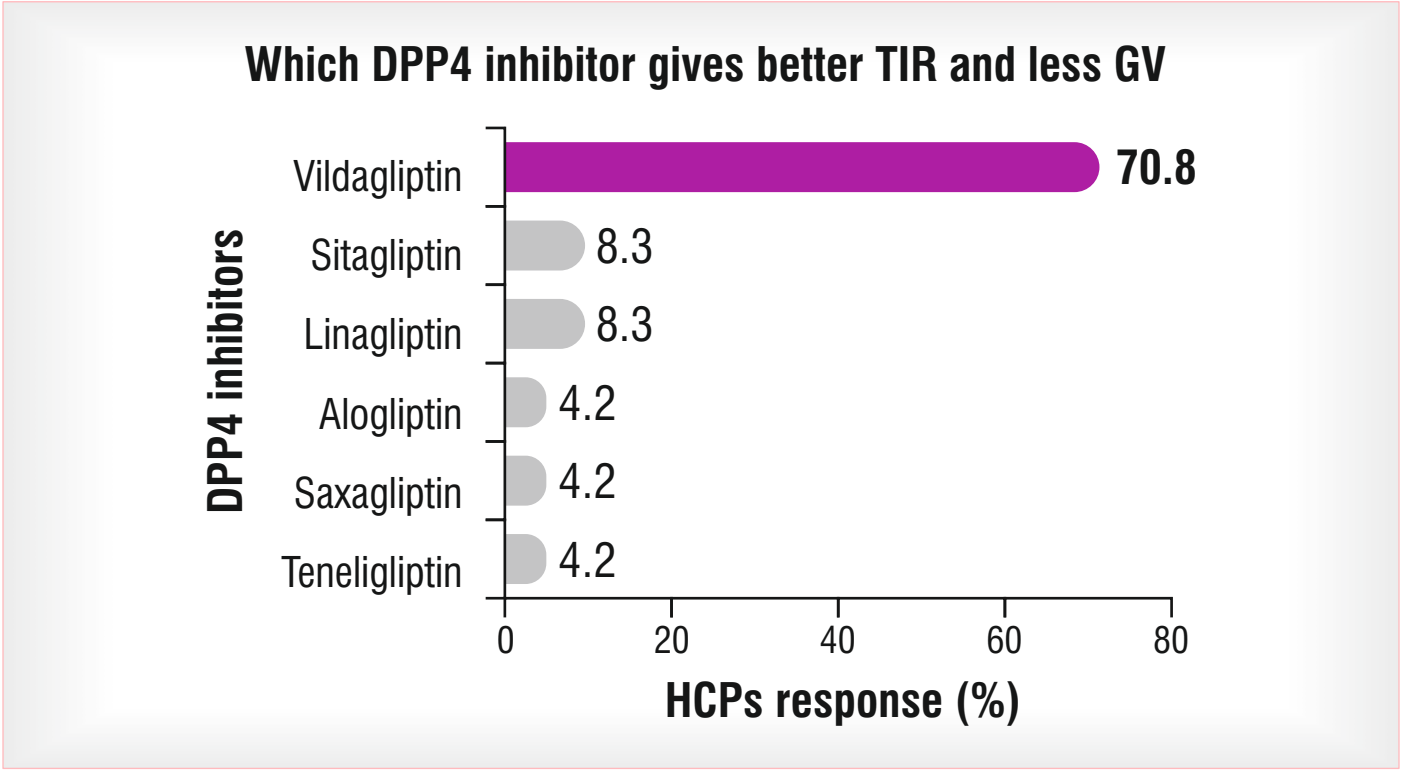
Dipeptidyl peptidase-4 (DPP-4) inhibitors have been widely accepted since they were introduced in 2006 due to their favorable safety profile, particularly their lack of weight gain and hypoglycemia risks.

Compared to other DPP-4 inhibitors, vildagliptin has the highest binding capacity for human DPP-4 enzyme, which induces more levels of active glucagon like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) incretins that substantially enhance the pancreatic islet α- and β-cell responsiveness to glucose, leading to a better TIR profile. Among all the DPP-4 inhibitors, the ability to block the inactivation of GLP-1 and GIP between meals and overnight was only demonstrated by vildagliptin. Moreover, vildagliptin is more potent than other DPP-4 inhibitors, such as sitagliptin, saxagliptin, linagliptin, and alogliptin, in suppressing glucagon, and causes less glycemic variability.

The patient's adherence to vildagliptin was also higher due to its low risk of hypoglycemia and other adverse effects; which makes vildagliptin a more suitable oral hypoglycemic agent in the elderly population. Vildagliptin exhibits the same metabolic advantages in subjects with impaired glucose tolerance as it does in T2DM. Vildagliptin thereby enhances islet function, which in turn enhances glucose metabolism. This therapy has also been linked to

advantageous extra-pancreatic effects, such as enhanced postprandial triglyceride-rich lipoprotein metabolism and enhanced peripheral insulin sensitivity. Additionally, a comprehensive meta-analysis of CV events adjudicated independently has also provided reassurance about the CV safety of DPP-4 inhibitors, particularly vildagliptin. Furthermore, real-world studies indicate that vildagliptin had a good safety profile without increased risk of CVD including chronic heart failure and hospitalization for heart failure (HHF) in patients with T2DM. Overall data indicate that vildagliptin has optimal glycemic control, better TIR, glycemic variability control as well as a CV neutral effect in patients with T2DM.

In one of the recent consensus study done in India the healthcare professionals (HCPs) strongly agreed with the consideration of TIR and glycemic variability as important clinical criteria for selecting antidiabetic therapy in patients with risks of macrovascular complications. The majority of HCPs experienced that vildagliptin gives better TIR and less glycemic variability compared to other DPP4 inhibitors. The study data demonstrated patients on vildagliptin spent an additional 13% (3 Hours) of time in the target range as compared to sitagliptin.



A significant reduction in glycemic variability was seen with vildagliptin, including the mean amplitude of glycemic excursion, a standard deviation of 24 hours glucose measured by continuous glucose monitoring, as well as glycosylated hemoglobin (HbA1c) and fasting prandial glucose. Consequently, glucose excursion may be attenuated glucose-dependently with DPP-4 inhibition, thus reducing glycemic variability markers.

Vildagliptin add-on to insulin therapy can improve glycemic control with minimal hypoglycemic risk when used in conjunction with self-monitoring of blood glucose. Moreover, this combination reduces the dose of insulin and was found to be well-tolerated when followed up for two years.

Overcoming glycemic variability and ensuring maximum time to be spent in the target range are important aspects for optimization of better clinical outcomes; Vildagliptin is the current choice of treatment that can help to address these aspects because of its better TIR maintenance.

Source: World Journal of Advanced Research and Reviews, 2023, 17(02), 001–009; Heliyon. 2021 Jan 15;7(1):e05967. doi: 10.1016/j.heliyon.2021.e05967.

CILNIBLU (CILNIDIPINE) WITH N-CHANNEL SELECTIVITY, FOR THE TREATMENT OF RAYNAUD'S

Raynaud's phenomenon was named after French physician Maurice Raynaud (1834-1881) and was first described in 1862. Raynaud's phenomenon is a disorder whereby blood vessels in the fingers and toes constrict and reduce blood flow, causing pain and discolouration. This is usually in response to cold exposure or emotional stress. It is either primary (idiopathic) or secondary (underlying disease). For people with Raynaud's phenomenon who do not respond to conservative measures (e.g. keeping warm), calcium channel blockers (CCBs) represent the first line in drug treatment.

Cilnidipine is a small molecule that targets different Calcium voltage gated channels (Cav 1.2 and Cav 2.2 channels).

Cav1.2 channels are voltage gated channels found in various tissues, including the heart and smooth muscle cells. By blocking these channels the influx of calcium ion into the cells can be reduced affecting the cellular processed and physiological functions regulated by calcium signaling. These agents which block these Cav 1.2 may be used as therapeutic agents for conditions such as hypertension, cardiac arrhythmias etc.

On the other hand, Cav 2.2 channels are distributed primarily in the central nervous system and play a crucial role in the release of neurotransmitter. By blocking these channels these blockers can modulate the release of norepinephrine, glutamate and substance P.This can have therapeutic implications in chronic pain, epilepsy and other neurological conditions.

With its ability to target Cav 1.2 and Cav 2.2 channels, Cilnidipine offers therapeutic benefits in the treatment of hypertension, Raynaud Disease, Sclerotylosis, Complex Regional Pain Syndromes, Neuralgia, and Scleroderma.

RECONNOITER-1 is a two-part, planned 76 patient trial which has inferred usefulness of cilnidipine for the treatment of Raynaud's and other symptoms in patients with systemic sclerosis. Cilnidipine-only treated patients had a reduction in weekly attacks of 42.2% versus 18.9%.The dosages of 10 mg and 20 mg were administered and both these dosages were well tolerated. Cilnidipine appears superior in safety to commonly used CCBs and seems to be more favorable for treatment of Raynaud's and other symptoms associated with systemic sclerosis. This work suggests the drug might have additional development opportunities in other peripheral neuropathic pain treatments.

The dual N-type and L-type calcium channel blocker, selective for the N-type calcium channel such as cilnidipine, enables the use of lower dose of phosphodiesterase type 5 inhibitor (PDE5) such as tadalafil, which shall improve the tolerability, is being explored for treatment of Raynaud's disease.

Cilnidipine, a dual calcium channel blocker with selectivity for N-type as well appears to be superior amongst CCBs and potential option with low dose PDE5 inhibitor for Raynaud's.

Source: Annals of the Rheumatic Diseases 2023; 82:962.

MEGO (MECOBALAMIN) IN THE MANAGEMENT OF CHRONIC PAIN IN FIBROMYALGIA

Fibromyalgia (FM) is a clinical entity characterized by widespread physical and psychological symptoms that includes chronic diffuse pain, fatigue, sleep, mood and cognitive disturbances and worldwide it affects approximately 0.4% to 9.3% of the population. Although the exact pathophysiology of the disease has remained unknown, central nervous system (CNS) sensitization has been proposed as the prominent or exclusive pathway in FM pathogenesis. Central sensitization, which refers to the amplification of pain by CNS mechanisms, presents clinically as pain hypersensitivity and allodynia (feeling pain in response to normally non-painful stimulus). For many patients suffering from FM, the current state of treatment with antidepressants and antiepileptics is unsatisfactory due to side effects.

Alternatively, more conservative treatment approaches have shown increasing benefit with correlations existing between nutrition and symptoms of chronic pain.

Research has shown that the symptoms associated with FM can be greatly reduced with **Vitamin B12.** Vitamin B12 can potentially exert its analgesic effect and psychological modulation through several complex pathways. Preclinical studies have shown that cobalamin inhibits glutamate exocytosis, as an excitatory pain neurotransmitter, and when infused intracerebroventricularly, increases GABA cell contents, as an inhibitory pain neurotransmitter. Vitamin B12 also upregulates brain-derived neurotrophic factor (BDNF) and increases nerve conduction velocity, which may reflect part of the regeneration process and brain plasticity. Another potential mechanism for the pain-reducing properties of vitamin B12 comes from interactions with prostaglandin synthesis, including cyclooxygenase (COX) enzymes. Preclinical studies showed simultaneous anti-inflammatory along analgesic effects on both peripherally and centrally induced pain models. One clinical study examined FM patients' self-reported response after B12 injection and found symptom relief. Another study examining the analgesic effects of vitamin B12 found that individuals receiving an intramuscular injection of Mecobalamin three times a week for 2 weeks showed a statistically significant decrease in reported pain scores as compared to a control group receiving normal saline for an equivalent time.

So, studies showed that vitamin B12 is an essential micronutrient involved in the preservation of pain inhibitory and excitatory neurotransmitters balance, inflammation moderation, and consequently in the diverse behavioral process including sleep, learning, memory, and sensation of pain.

Based on this, Vitamin B12 could be an adjunctive therapy in FM patients who suffer from nociplastic pain and other central symptoms such as fatigue, sleep, and cognitive disturbance.

Source: Haddad HW, et al. Pain Ther (2021) 10:827–848; Gharibpoor F, et al. BMC Rheumatology. 2022; 6:51.

EXCEL

Dr. Prabhu Kasture (MD, DPH)

Dy. Director Medical Services & Pharmacovigilance

PHONE NO.: 022-66638043

EMAIL: prabhu.k@bluecrosslabs.com

Correspond: Blue Cross Laboratories Pvt. Ltd. (Peninsula Corporate Park, Peninsula Chambers, Ganpatro Kadam Marg, Lower Parel, Mumbai-400013

http://www.bluecrosslabs.com/