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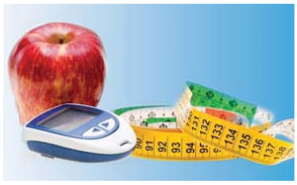

BEXIMCO PHARMA here's to life

Treatment Maintenance Duration of Dual Therapy with Metformin and Sitagliptin in Type 2 Diabetes: The ODYSSEE Observational Study

Type 2 diabetes (T2DM) is a major public-health challenge and is associated with significant morbidity and mortality, which are mostly attributable to long-term cardiovascular complications of the disease. Nevertheless, the risk of long-term complications can be significantly reduced by improving glycemic control. This observational study (ODYSSEE) was undertaken to compare dual therapy with metformin and sitagliptin, a dipeptidyl peptidase (DPP)-4 inhibitor, with dual therapy with metformin and a sulphonylurea in patients failing to respond adequately to metformin monotherapy. As a comprehensive measure of efficacy, the study evaluated treat-ment maintenance duration, defined as the time from starting treatment until the physician chose to change the treatment. The primary objective of the present study was to assess whether metformin plus sitagliptin dual therapy was superior to metformin plus sulphonylurea dual therapy in terms of treatment maintenance duration in patients with T2DM. Secondary objectives were to describe treatment regimens using sitagliptin in standard clinical practice and the profiles of such treated patients, and to document the evolution of the clinical status of such patients during treatment. Information on the treatment regimens and patient profiles are to be presented elsewhere. The study compared the duration of maintenance of treatment in patients with T2DM using dual therapy with either metformin and sitagliptin (M-Sita) or metformin and a sulphonylurea (M-SU). This observational study included adult patients with T2DM who had responded inadequately to metformin monotherapy and therefore had started de-novo treatment with Met-Sita or Met-SU within the previous eight weeks. Patient follow-up and changes to treatment were performed according to their general practitioner's usual clinical practice. The primary outcome was time to change in treatment for whatever cause. The HbA1c and symptomatic hypoglycemia were also documented. The results of the study shows that the median treatment duration for patients in the M-Sita group (43.2 months) was significantly longer ($P < 0.0001$) than in the M-SU group (20.2 months). This difference persisted after adjusting for baseline differences and confounders. A similar reduction in HbA1c was noted in both arms (–0.6%), and the incidence of hypoglycemia prior to treatment modification was lower with M-Sita (9.7%) than with M-SU (21.0%). Adverse events potentially related to treatment were reported in 2.8% (n = 52) and 2.7% (n = 20) of patients in the M-Sita and M-SU arms, respectively. The study concludes that under everyday conditions of primary diabetes care, dual therapy with M-Sita can be maintained for longer than M-SU. In addition, while efficacy, as measured by changes in HbA1c, was similar between treatments, the incidence of hypoglycemia was lower in patients taking M-Sita.

ARTICLES INSIDE

Bexinfo-Diabetology is a publication aimed to present the current noticeable happenings of diabetes from most authentic sources. Our effort will be successful only if it can meet some of your needs of knowledge in your daily practice.

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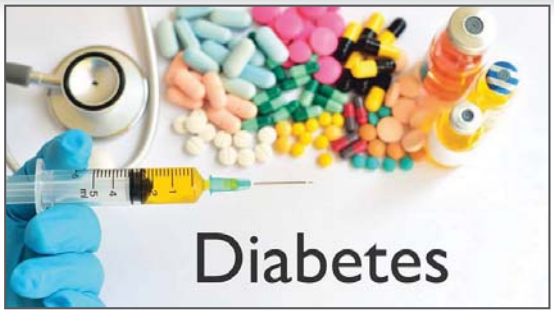
Intensive Medical Treatment Can Reverse Type 2 Diabetes



Type 2 diabetes can be reversed with intensive medical treatment using oral medications, insulin and lifestyle therapies, according to a study published in the Endocrine Society's *Journal of Clinical Endocrinology & Metabolism*. Type 2 diabetes is typically thought of as a chronic condition. As it progresses, individuals with type 2 diabetes often need to use a healthy diet, exercise and an increasingly complex combination of medications to manage the condition. "By using a combination of oral medications, insulin and lifestyle therapies to treat patients intensively for two to four months, we found that up to 40 percent of participants were able to stay in remission three months after stopping diabetes medications," said the study's first author. To study ways to put type 2 diabetes into remission, the researchers randomly divided 83 individuals with the condition into three study groups. Two of the groups received an intensive metabolic intervention where they were provided with a personalized exercise plan and a suggested meal plan that reduced their daily calorie intake by 500 to 750 calories a day. These study participants met regularly with a nurse and dietitian to track their progress and received oral medications and insulin at bedtime to tightly manage their blood glucose levels. One group underwent the intervention for eight weeks, while the other was treated intensively for 16 weeks. After the intervention, individuals in both groups stopped taking diabetes medications and were encouraged to continue with lifestyle changes. The two intervention groups were compared to a control group of individuals with type 2 diabetes. Participants in this group received standard blood sugar management advice from their usual healthcare provider for the duration of the trial, and they received standard lifestyle advice. Participants in all three groups received usual diabetes care if they experienced a diabetes relapse. Study participants had their average blood glucose levels from the past two to three months measured using a HbA1C blood test at eight, 20, 28 and 52 weeks to gauge how well their blood sugar was controlled. They also undertook oral glucose tolerance tests. Three months after the intervention was completed, 11 out of 27 individuals in the 16-week intervention group met HbA1C criteria for complete or partial diabetes remission, compared to four out of 28 individuals in the control group. Three months after finishing the eight-week intervention, six out of 28 individuals in that group met the same criteria for complete or partial diabetes remission. "The research might shift the paradigm of treating diabetes from simply controlling glucose to an approach where we induce remission and then monitor patients for any signs of relapse," McInnes said. "The idea of reversing the disease is very appealing to individuals with diabetes. It motivates them to make significant lifestyle changes and to achieve normal glucose levels with the help of medications. This likely gives pancreas a rest and decreases fat stores in the body, which in turn improves insulin production and effectiveness." The senior investigator on the trial, added, "We chose to use metformin, acarbose and basal insulin glargine in this trial as these medications have all been shown to slow or prevent the development of type 2 diabetes. However, other drug combinations could lead to higher remission rates and need to be systematically studied with regard to this outcome."

Study Suggests New way to Prevent Vision Loss in Diabetics and in Premature Infants

ligand for antiangiogenic therapy of diabetic retinopathy," which will be published in *The Journal of Experimental Medicine,* suggests that inhibiting this molecule may prevent similarly aberrant blood vessels from damaging the vision of not only diabetics, but also of premature infants. Changes in the vasculature of diabetes patients can cause long-term complications such as diabetic retinopathy, which affects around 93 million people worldwide. Many of these patients suffer a dramatic loss of vision as the blood vessels supplying the retina become leaky and new, abnormal blood vessels are formed to replace them. A molecule called vascular endothelial growth factor (VEGF) regulates blood vessel growth and leakiness, and two VEGF inhibitors, ranibizumab and aflibercept, have been approved to treat retinal vascular leakage, though they are only successful in about a third of patients. The growth of abnormal new blood vessels also causes retinopathy of prematurity (ROP), the most common cause of vision loss in children that affects up to 16,000 premature infants per year in the US. vascular endothelial growth factor inhibitors are not approved for use in these patients because VEGF is crucial for vascular development in newborn children. Study lead-author and his colleagues at Bascom Palmer developed a technique called "comparative ligandomics" to identify additional molecules that regulate the behavior of blood vessels in diabetic mice. The approach allows the researchers to compare the signaling molecules that selectively bind to the surface of retinal blood vessel cells in diabetic but not healthy animals. "It is estimated that between one third and one half of all marketed drugs act by binding to cell surface signaling molecules or their receptors," says Li. "Our ligandomics approach can be applied to any type of cell or disease to efficiently identify signaling molecules with pathogenic roles and therapeutic potential." Using this technique, Li and colleagues discovered that a protein called secretogranin III (Scg3) efficiently binds to the surface of retinal blood vessel cells in diabetic, but not healthy, mice. Though Scg3 promotes the secretion of hormones and other signaling factors, it wasn't thought to have a signaling function itself. Nevertheless, the researchers found that Scg3 increased vascular leakage, and, when administered to mice, it stimulated blood vessel growth in diabetic, but not healthy, animals. Vascular endothelial growth factor, in contrast, stimulates blood vessel growth in both diabetic and healthy mice. Li and colleagues think that Scg3 binds to a distinct cell surface receptor that is specifically up-regulated in diabetes. Treating diabetic mice with Scg3-neutralizing antibodies dramatically reduced the leakiness of their retinal blood vessels. Moreover, the antibodies significantly inhibited the growth of new blood vessels in mice with oxygen-induced retinopathy, a well-established animal model of human ROP. Though the researchers still need to confirm the role of Scg3 in humans, inhibiting this protein could be an effective treatment for both diabetic retinopathy and ROP, especially as it appears to have no role in normal vascular development. The researcher says-"Scg3 inhibitors may offer advantages such as disease selectivity, high efficacy, and minimal side effects". "Because they target a distinct signaling pathway, anti-Scg3 therapies could be used in combination with, or as an alternative to, VEGF inhibitors"-he added.

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Researchers "Very Concerned" About Prediabetes Epidemic

The Centers for Disease Control and Prevention (CDC) says more than one in three Americans have blood-sugar levels that raise their risk of developing the disease. It's called prediabetes -- and doctors say it's an epidemic that's out of control. Researchers at University of California, Los Angeles (UCLA) estimate nearly half of all adults in California have prediabetes or undiagnosed diabetes: 46% of all adults, and 33 % of young adults between the ages of 18 and 39 years. "The rates are very high, surprisingly high," researcher who co-authored the report, told. "We're very concerned about the rates among the young adults because of their increased risk of developing type 2 diabetes, which sets them on this path for some serious complications in the future." Complications include blindness, heart and kidney disease and premature death. Without intervention, about 70% of those with prediabetes eventually develop diabetes. With intervention, it doesn't have to progress to the full-blown disease, according to the researchers. "The most effective way to prevent progression of prediabetes to diabetes is through diet and exercise -- regular activity, watching carbohydrate intake," said the researcher. Paul Healy, 52, was diagnosed with prediabetes in 2010 and then diabetes. Since then, he has changed his diet and lost 32 pounds. "Part of what happened, when I was diagnosed, is that I was really in denial about it," Healy said. "So, it took me awhile to really get my blood sugars under the control and learn how to say no." The CDC estimates 90% of people with prediabetes don't know they have it. But a simple blood test could quickly make the diagnosis. That's crucial because, more than half the time, diet and exercise can prevent prediabetes from progressing to diabetes.

Voglibose may Reduce Type 2 Diabetes Mellitus Development

The increased prevalence of type 2 diabetes mellitus is a major concern for health providers. Voglibose, an α-glucosidase inhibitor, could prevent the development of type 2 diabetes in high-risk Japanese individuals with impaired glucose tolerance. Patients who have impaired glucose tolerance and who are at high risk for developing type 2 diabetes are less likely to do so if they are treated with voglibose compared with placebo, according to a study published in the journal The Lancet. The study enrolled 1780 eligible patients on a standard diet and taking regular exercise with impaired glucose tolerance were randomly assigned to oral voglibose 0·2 mg three times a day (n=897) or placebo (n=883) in a multi-centre, double-blind, parallel group trial. Treatment was continued until participants developed type 2 diabetes (primary endpoint) or normoglycemia (secondary endpoint), or for a minimum of 3 years, subject to the findings of an interim analysis. Analysis was by full analysis set. In the interim analysis, voglibose was better than placebo (P=0·0026) in individuals treated for an average of 48·1 weeks (SD 36·3). Patients treated with voglibose had a lower risk of progression to type 2 diabetes than did those on placebo (50 of 897 *vs* 106 of 881; hazard ratio 0·595, 95% CI 0·433–0·818; P=0·0014). More people in the voglibose group achieved normoglycemia than did those in the placebo group (599 of 897 *vs* 454 of 881; 1·539, 1·357–1·746; P<0·0001). Eight hundred and ten (90%) of 897 patients in the voglibose group had adverse events *versus* 750 (85%) of 881 in the placebo group. Serious adverse events (all one each) in the voglibose group were cholecystitis, colonic polyp, rectal neoplasm, inguinal hernia, liver dysfunction, and subarachnoid hemorrhage, and in the placebo group were cerebral infarction and cholecystitis. The study concludes that voglibose, in addition to lifestyle modification, can reduce the development of type 2 diabetes in high-risk Japanese individuals with impaired glucose tolerance.

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Linagliptin Controlled Type 2 Diabetes in Asian

Asia is home to more than 200 million patients with diabetes, predominantly type 2 diabetes mellitus. In Asian patients, type 2 diabetes occurs at a younger age with relatively low body mass index (BMI), and also with a lower risk threshold for complications than in Western populations. Dipeptidyl peptidase-4 (DPP-4) inhibitors promote insulin secretion in a glucose-dependent manner by prolonging the half-life of the incretin hormone glucagon-like peptide-1 (GLP-1). In addition, DPP-4 inhibitors might improve regulation of glucagon secretion from pancreatic a-cells. Linagliptin is a potent, highly reversible binding to protein and selective DPP-4 inhibitor with a predominantly non-renal elimination, enabling it to be prescribed in a single 5-mg once-daily dose to patients with type 2 diabetes without dose change regardless of renal and liver function. In multinational phase III clinical trials that included Asian as well as Western patients, linagliptin reduced hyperglycemia without showing an increased propensity to cause weight gain or hypoglycemic events when used as a monotherapy or with other oral glucose-lowering drugs. In a pooled subgroup analysis of these studies, linagliptin was shown to be an efficacious and well-tolerated treatment option for South and East Asian patients with inadequately controlled type 2 diabetes. A subgroup analysis of a phase III trial of linagliptin added to metformin and a sulfonylurea showed that the combination was efficacious and well tolerated by Chinese patients. The mechanism of action of DPP-4 inhibitors, such as linagliptin, addresses challenges endemic to Asian type 2 diabetes populations. Specifically, carbohydrate-rich diets causing elevation of post-prandial glucose (PPG) and glycemic variability are seen as a key factor in Asians, and DPP-4 inhibitors primarily affect control of PPG excursions. Although this trial did not include meal tolerance testing, statistically significant reductions in 2-h PPG with linagliptin have been shown in a population of Asian patients pooled from four phase III trials. In that analysis, linagliptin reduced PPG by a placebo-corrected –56.9 mg/dL (95% CI –85.17, –28.52)The present randomized, phase III, placebo-controlled, double-blind, 24-week study evaluated the DPP-4 inhibitor, linagliptin, as monotherapy in Asian patients with inadequately controlled type 2 diabetes mellitus. Patients who were treatment naıve or had been treated with one oral anti-diabetes drug were randomized to either linagliptin 5 mg daily or a placebo after washout. The primary end-point was a change from baseline in glycated hemoglobin after 24 weeks. A total of 300 Asian (87% Chinese) patients with type 2 diabetes mellitus were randomized to linagliptin or placebo at a 2:1 ratio. After 24 weeks of treatment, adjusted mean (standard error) glycated hemoglobin decreased by a placebo-corrected - 0.50 ± 0.11 ($P < 0.0001$). In patients with baseline glycated hemoglobin ≥8.5%, the placebo- corrected decrease in glycated hemoglobin was -0.91 ± 0.20% ($P < 0.0001$). Adverse events occurred in 28.0 and 28.3% of linagliptin and placebo patients, respectively, but few were drug-related (3.0 and 2.0%, respectively). Hypoglycemia was reported by one linagliptin patient and no placebo patients. Treatment with linagliptin was weight neutral. The study concludes that linagliptin monotherapy was efficacious and well tolerated over 24 weeks in Asian patients with type 2 diabetes who were treatment naıve or had been previously treated with one oral anti-diabetes drug.

Metformin Still Best as First Type 2 Diabetes Treatment

Newly updated guidelines reaffirm that metformin is the first-line drug for people with type 2 diabetes, and that several other medications -- including newer ones -- can be added if needed. The recommendations come from the American College of Physicians (ACP). The American Academy of Family Physicians endorsed the new guidelines. The ACP updated the guidelines because of new research into diabetes drugs, and the U.S. Food and Drug Administration approval of new diabetes drugs. "Metformin, unless contraindicated, is an effective treatment strategy because it has better effectiveness, is associated with fewer adverse effects, and is cheaper than most other oral anti-diadetic drugs," said the researchers news release. "The escalating rates of obesity in the U.S. are increasing the incidence and prevalence of diabetes substantially. Metformin has the added benefit of being associated with weight loss," the researcher said. The ACP recommends that if a patient needs to take a second drug by mouth to lower blood sugar levels, physicians should look at adding a sulfonylurea, thiazolidinedione, sodium-glucose co-transporter-2 (SGLT-2) inhibitor, or a Dipeptidyl peptidase-4 (DPP-4) inhibitor. Examples of sulfonylurea drugs include glyburide, glimepiride, glipizide and tolbutamide. Thiazolidinedione drugs include pioglitazone and rosiglitazone. Sodium-glucose co-transporter 2inhibitors include canagliflozin, empagliflozin and dapagliflozin. Dipeptidyl peptidase-4 inhibitors include sitagliptin or linagliptin. "Adding a second medication to metformin may provide additional benefits," said the researcher. "However, the increased cost may not always support the added benefit, particularly for the more expensive, newer medications. American College of Physicians recommends that clinicians and patients discuss the benefits, adverse effects, and costs of additional medications," he added. An estimated 29 million people in the United States have diabetes, according to the U.S. Centers for Disease Control and Prevention. The guidelines are published in the journal the *Annals of Internal Medicine*.

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