

Vildagliptin Improves Blood Sugar Control

Monotherapy and combination trials maintain control over time, according to multiple studies.

BY RYAN DUBOSAR, CONTRIBUTING EDITOR

Vildagliptin improves blood sugar control when used as monotherapy or in combination treatment, according to research presented at the American Diabetes Association's 66th Scientific Sessions in Washington, DC.

Ameet Nathwani, PhD, Global Therapy Area Head, Cardiovascular, Metabolism and Atherosclerosis at Novartis, summarized a series of posters, abstracts and oral presentations during the late-breaking sessions. Vildagliptin (Galvus; Novartis, Basel, Switzerland) is in the DPP-4 class of glucose inhibitors. It works by targeting pancreatic islet dysfunction, a cause of high blood sugar levels in patients with type 2 diabetes. Vildagliptin affects pancreatic alpha and beta cells, reducing sugar production from the liver and increasing insulin production.

Islet dysfunction and insulin resistance both contribute to diabetes. Islet dysfunction can lead to excess sugar production via glucagon from the alpha cells and reduced insulin from the beta cells.

"We're very excited that we've got clinical data that supports the mechanism that's behind the benefit that we're seeing in patients," he said, later adding, "We're very excited by the islet cell effects, and we think that they may well be a potential for disease modification that we intend to explore much further."

Vildagliptin is rapidly absorbed and has a bioavailability of >80%, Dr. Nathwani said. It has low protein binding of <20%. It is metabolized predominately by hydrolysis and does not induce or utilize the P450 system. The drug is excreted mainly in the inactive metabolite form into urine, and there is no interaction with other commonly prescribed drugs. Researchers do not expect special dose regimens for the elderly or the renally impaired.

MONOTHERAPY USES

Vildagliptin is being investigated as a once-daily drug at 100 mg. Other dosing regimens have been studied and are "absolutely equivalent" in terms of glycemia, Dr. Nathwani reported. Vildagliptin research included more than 5,400 patients in phase 2 and phase 3 trials, and more than 4,500 were exposed to vildagliptin with 637 patients exposed to the agent for ≥ 1 year.

Overall, there was no weight gain in the vildagliptin patients, regardless of body mass index (BMI). There was a weight gain of 2.8 kg in obese patients treated with thiazolidinedione (TZD), "which is very reassuring that that weight change we see in the shorter studies is sustained out to 1 year," Dr. Nathwani said.

Gastroenterological tolerability, in particular, diarrhea and nausea, were better in vildagliptin-assigned patients. "The adverse event profile is comparable to placebo," Nathwani said. "We really have a well-tolerated drug."

DRUG IN CLINICAL USE

A comparative study involving 780 treatment-naïve patients compared vildagliptin to metformin and confirmed vildagliptin provides clinically meaningful and sustained reduction in blood sugar with significantly fewer side effects. While both groups achieved clinically and statistically significant reductions from baseline in HbA1c levels of 1.1% and 1.4%, the vildagliptin group had a 21.8% incidence of side effects compared with a 43.7% rate among patients taking metformin.

A realistic clinical use of vildagliptin is as an add-on to metformin, Dr. Nathwani said. A 6-month, 416-patient study compared blood sugar control as measured by HbA1c among people taking metformin alone or

vildagliptin plus metformin. Patients taking a combination regimen experienced a 1.1% drop in blood sugar levels compared with metformin alone.

There was no difference in results among elderly patients, "which is very important given the need for one drug to control patients in this group," Dr. Nathwani said.

Patients coming into the study had a very high background rate of gastroenterological adverse events despite the fact that they had been on metformin for quite a considerable period of time. The fewer side effects "are interesting, and we'll continue to explore if there's a real rationale or mechanism behind this," Dr. Nathwani said.

Late-breaking data presented at the meeting showed results of combining vildagliptin with TZD. The four-arm study measured results of treatment with 100 mg vildagliptin, 30 mg pioglitazone, the two doses combined, and a combination of 50 mg vildagliptin and 15 mg pioglitazone. The 6-month trial evaluated 592 patients who were treatment-naïve and had a baseline HbA1c between 7.5% and 11%.

Of all patients, the combination regimen saw a statistically significant reduction of 1.9% compared with a 1.4% reduction among patients on pioglitazone alone. Among patients with a baseline HbA1c of 9% or more, the combination regimen produced a 2.8% reduction.

Nearly two-thirds of patients starting both drugs together achieved the ADA's goal of <7% HbA1c levels. Nearly 50% of patients who had a baseline of nearly 10% reached the target of <7%.

Elderly patients aged ≥ 65 years had a reduction of 2.3% from a mean baseline of 8.4%. The mean HbA1c control at the end of 6 months was 6.2%, nearly the upper limit of normal. In obese patients with a BMI >35, the combination regimen results in a decline in HbA1c of 2.2% from a mean baseline of 8.6%.

In summary, Dr. Nathwani said that vildagliptin is a potent and highly selective DPP-4 inhibitor with "robust efficacy" in monotherapy compared to a TZD and in combination with metformin or a TZD. The drug is highly efficacious in combination therapy, and the results have been shown out to 1 year. Tolerability is comparable to placebo, gastroenterological tolerability is superior to metformin, and there was no weight gain overall. ■

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Nathwani A. The Use of Vildagliptin for Treatment of Patients with Type 2 Diabetes. Late-breaking clinical trials. Presented at the American Diabetes Association's 66th Scientific Sessions. June 9-13, 2006. Washington, DC.

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