Sitagliptin: The First in a New Class of DPP-4 Inhibitors for the Treatment of Type 2 Diabetes

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ABSTRACT

Published on 30th September 2008

Sitagliptin (JANUVIA®) is the first approved DPP-4 inhibitor for the treatment of T2DM and is approved in over 60 countries worldwide. Sitagliptin is a potent, highly selective and fully reversible DPP-4 enzyme inhibitor that was developed to treat T2DM. Sitagliptin is well-absorbed following oral administration, with a half-life of approximately 12 hours, supporting once-daily administration.

Methodology: Metaanalysis of Stialiptin on Type II diabetes mellitus patients.

Result: A single daily dose achieves 24-hour DPP-4 inhibition that peaks within 2 to 4 hours and maintains at least 80% DPP-4 inhibition over the full 24-hour dosing period. Food does not affect the pharmacokinetics, and the drug exhibits low protein binding, with no clinically important drug-drug interactions.

Keywords: Sitagliptin' Januvia monotherapy, T2DM, Glycemic control

*See End Note for complete author details

Clinical Efficacy and Tolerability

Clinical trials in patients with T2DM have shown that once daily sitagliptin, either as monotherapy, or added to other oral antihyperglycemic agents, provided substantial improvements in overall glycemic control, with clinically meaningful HbA1c reductions across a range of baseline HbA1c levels, and also lowered both fasting and postprandial glucose levels and improved several parameters of b-cell function.

Proof of clinical concept was demonstrated by an oral glucose tolerance crossover study in T2DM patients in which a single dose of sitagliptin provided sustained 24-hour DPP-4 inhibition, doubled active GLP-1 and GIP levels, increased insulin, and decreased glucagon levels, with a consequent reduction in glycemic excursion following a glucose load demonstrated at 2 and 24 hours.[1]

Three randomized, double-blind, placebo controlled trials—2 multinational studies of 18 and 24 weeks each, and a 12-week trial in Japan—evaluated the clinical efficacy of sitagliptin monotherapy in patients who had T2DM for approximately 4 years at baseline. Although about half of the trial subjects were already on other oral antihyperglycemic treatments, more than 50% still had HbA1c above 8%. Once-daily sitagliptin consistently and significantly reduced HbA1c levels vs placebo across all 3 trials, and both fasting blood glucose levels and the postprandial glucose spikes also decreased.[2-4] In the 18- and 24-week trials, HbA1c reductions were progressively greater among patients from increasingly elevated baseline HbA1c levels. Sitagliptin improved markers of b-cell function in the 24-week study (HOMA-b, proinsulin/insulin ratio),[3] and pooled monotherapy data indicated an improved b-cell response to glucose in a model-based assessment of b-cell function.[5]

In a multifactorial randomized study evaluating each agent independently and in combination, a combination of sitagliptin 50 mg BID with metformin 1000 mg BID produced a significant placebo-subtracted drop in HbA1c from baseline of 2.1%, with a high proportion (67%) of patients achieving HbA1c <7% and substantial improvements in fasting plasma glucose and 2-hour postprandial glucose. Patients who received sitagliptin 50 mg/metformin 1000 mg BID in the open-label treatment arm, for those with higher initial baseline HbA1c values (>11%), recorded an HbA1c reduction of 2.9%.[6]

Further multinational, randomized controlled trials assessed the clinical efficacy of once-daily sitagliptin as an add-on to monotherapy with either metformin or pioglitazone in T2DM patients with mean baseline

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HbA1c approximately 8% who were inadequately controlled by those agents.[7,8] In these trials sitagliptin provided additional incremental HbA1c reductions of approximately 0.7% beyond that achieved with either continued treatment with metformin or pioglitazone alone. Once-daily sitagliptin approximately doubled the proportion of patients achieving target HbA1c of less than 7% relative to placebo, both as monotherapy (41% vs 17%; P<0.01)[3] and when added to either metformin (47% vs 18%; P<0.01)[7] or pioglitazone (45% vs 23%; P<0.01).[8]

Sitagliptin was generally well tolerated across clinical trials involving more than 6000 patients, with an overall safety profile similar to placebo.[1-4, 6-13] The effect of sitagliptin on body weight was generally neutral, with little change from baseline as monotherapy and weight change similar to placebo in combination studies with metformin or pioglitazone.

In a 52-week noninferiority trial vs the sulfonylurea glipizide on a background of metformin,[9] once-daily sitagliptin produced a comparable reduction in HbA1C with progressively greater reductions up to 1.7% for high-baseline patients, however, patients treated with sitagliptin experienced significantly fewer hypoglycemic episodes (5% vs 32%, P<0.001) and modest weight loss (-1.5 kg), in contrast to the weight gain induced by glipizide (+1.1 kg).

END NOTE

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Conflict of Interest: None declared

Cite this article as: Karthik Anantharaman. Sitagliptin: The First in a New Class of DPP-4 Inhibitors for the Treatment of Type 2 Diabetes. Kerala Medical Journal. 2008 Sep 30;1(1):33-34

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