

Nuts, Dietary Pulses Improve Control in Type 2

BY KATE JOHNSON

MONTREAL — A diet rich in pulses and nuts can improve glycemic control in type 2 diabetes patients to within ranges seen with pharmaceutical intervention, researchers reported at the World Diabetes Congress.

A meta-analysis of 41 trials of pulses, either alone or combined with low glycemic or high fiber diets, noted im-

proved markers of long-term glycemic control (*Diabetologia* 2009;52:1479-95), reported Dr. John Sievenpiper of St. Michael's Hospital's risk factor modification center, Toronto.

Another study, also conducted by his group, found that 75 g of mixed nuts daily for 3 months improved blood lipids and glycemic control in patients with type 2 diabetes, compared with a mixture of nuts and muffins, or muffins alone. "Whatever

your favorite nut or form of nut, it's good to get it into your diet," said Dr. Cyril Kendall of the University of Toronto's department of nutritional sciences.

Both researchers acknowledged long lists of industry relationships: serving on advisory boards for a number of food companies, as well as the International Nut Council, and the Canola and Flax Councils of Canada, and receiving consultant fees from Pulse Canada.

Dietary pulses such as chickpeas, beans, lentils, and peas are characterized by a low glycemic index, high fiber content, high levels of amylose and resistant starches, and vegetable protein, and various other antinutrients "which may act as enzyme inhibitors," said Dr. Sievenpiper. "The effect is to decrease starch digestion and absorption and therefore postprandial glycemia."

His meta-analysis included 11 trials that examined consumption of pulses alone, which noted an overall decrease in standardized mean difference (SMD) of 0.71 in fasting blood glucose (FBG) and 0.62 in serum insulin. Similarly, 19 trials looking at consumption of pulses in low glycemic index (GI) diets noted an SMD decrease of 0.28 in glycosylated blood proteins (GP)—either hemoglobin A_{1c} or fructosamine. And in 11 trials examining pulses in high-fiber diets, there were SMD reductions in fasting blood glucose of 0.32 and in GP of 0.27.

Based on these results, "We would expect about a 0.48% reduction in HbA_{1c}, and this level of benefit approaches that seen with acarbose, exceeds the [Food and Drug Administration] proposed clinically meaningful threshold of 0.3%, and lies at the lower limit of efficacy of what you might expect for oral agents," Dr. Sievenpiper said.

The nut study randomized 117 patients with type 2 diabetes to consume either 75 g nuts, 38 g nuts and 1.5 bran muffins (150 kcal per muffin), or three muffins daily for 3 months. Nut portions included a mix of almonds, cashews, macadamias, pecans, pistachios, walnuts, and peanuts. All treatment portions were equivalent to 475 kcal/day and were designed to maintain rather than decrease body weight.

The primary outcome of the study was change in HbA_{1c} and serum lipids.

The patients' baseline characteristics were similar across the groups. They ranged in age from 61 to 63 years, 75% were male, ethnic backgrounds were diverse, and body mass index ranged from 28.8 to 30.3.

All patients were being treated with oral hypoglycemic medication, and their mean HbA_{1c} level was 7.1%. The mean duration of diabetes was 7-8 years. One hundred patients completed the study, with a similar dropout rate in each group.

An intention-to-treat analysis revealed that HbA_{1c} levels were significantly lower in the nuts-only group, compared with the nut-muffin combination group (6.88% versus 7.02%), although the latter was not significantly lower than the muffin-only group (7.06%), said Dr. Kendall.

There was a significant dose response seen in LDL cholesterol, which fell by 0.19 mmol/L in the full-nut group, compared with full-muffin group.

Previous studies have shown that "nuts are not entirely digested and there's an excretion of about 15%-20% that are simply not absorbed and pass through the gastrointestinal tract," Dr. Kendall said.

ONGLYZA™ (saxagliptin) tablets

RX ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

Monotherapy and Combination Therapy

ONGLYZA (saxagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [See *Clinical Studies* (14).]

Important Limitations of Use

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

ONGLYZA has not been studied in combination with insulin.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with ONGLYZA. [See *Adverse Reactions* (6.1).]

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Monotherapy and Add-On Combination Therapy

In two placebo-controlled monotherapy trials of 24-weeks duration, patients were treated with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, and placebo. Three 24-week, placebo-controlled, add-on combination therapy trials were also conducted: one with metformin, one with a thiazolidinedione (pioglitazone or rosiglitazone), and one with glyburide. In these three trials, patients were randomized to add-on therapy with ONGLYZA 2.5 mg daily, ONGLYZA 5 mg daily, or placebo. A saxagliptin 10 mg treatment arm was included in one of the monotherapy trials and in the add-on combination trial with metformin.

In a prespecified pooled analysis of the 24-week data (regardless of glycemic rescue) from the two monotherapy trials, the add-on to metformin trial, the add-on to thiazolidinedione (TZD) trial, and the add-on to glyburide trial, the overall incidence of adverse events in patients treated with ONGLYZA 2.5 mg and ONGLYZA 5 mg was similar to placebo (72.0% and 72.2% versus 70.6%, respectively). Discontinuation of therapy due to adverse events occurred in 2.2%, 3.3%, and 1.8% of patients receiving ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. The most common adverse events (reported in at least 2 patients treated with ONGLYZA 2.5 mg or at least 2 patients treated with ONGLYZA 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%). The adverse reactions in this pooled analysis reported (regardless of investigator assessment of causality) in ≥5% of patients treated with ONGLYZA 5 mg, and more commonly than in patients treated with placebo are shown in Table 1.

Table 1: Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Trials* Reported in ≥5% of Patients Treated with ONGLYZA 5 mg and More Commonly than in Patients Treated with Placebo

	Number (%) of Patients	
	ONGLYZA 5 mg N=882	Placebo N=799
Upper respiratory tract infection	68 (7.7)	61 (7.6)
Urinary tract infection	60 (6.8)	49 (6.1)
Headache	57 (6.5)	47 (5.9)

* The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with ONGLYZA 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo.

In this pooled analysis, adverse reactions that were reported in ≥2% of patients treated with ONGLYZA 2.5 mg or ONGLYZA 5 mg and ≥1% more frequently compared to placebo included: sinusitis (2.9% and 2.6% versus 1.6%, respectively), abdominal pain (2.4% and 1.7% versus 0.5%), gastroenteritis (1.9% and 2.3% versus 0.9%), and vomiting (2.2% and 2.3% versus 1.3%).

In the add-on to TZD trial, the incidence of peripheral edema was higher for ONGLYZA 5 mg versus placebo (8.1% and 4.3%, respectively). The incidence of peripheral edema for ONGLYZA 2.5 mg was 3.1%. None of the reported adverse reactions of peripheral edema resulted in study drug discontinuation. Rates of peripheral edema for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo were 3.6% and 2% versus 3% given as monotherapy, 2.1% and 2.1% versus 2.2% given as add-on therapy to metformin, and 2.4% and 1.2% versus 2.2% given as add-on therapy to glyburide.

The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for ONGLYZA (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The incidence rate of fracture events in patients who received ONGLYZA did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.

An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to ONGLYZA is not known.

Adverse Reactions Associated with ONGLYZA (saxagliptin) Coadministered with Metformin in Treatment-Naive Patients with Type 2 Diabetes

Table 2 shows the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients participating in an additional 24-week, active-controlled trial of coadministered ONGLYZA and metformin in treatment-naive patients.

Table 2: Initial Therapy with Combination of ONGLYZA and Metformin in Treatment-Naive Patients: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Treated with Combination Therapy of ONGLYZA 5 mg Plus Metformin (and More Commonly than in Patients Treated with Metformin Alone)

	Number (%) of Patients	
	ONGLYZA 5 mg + Metformin* N=320	Metformin* N=328
Headache	24 (7.5)	17 (5.2)
Nasopharyngitis	22 (6.9)	13 (4.0)

* Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

Hypoglycemia

Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. In the add-on to glyburide study, the overall incidence of reported hypoglycemia was higher for ONGLYZA 2.5 mg and ONGLYZA 5 mg (13.3% and 14.6% versus placebo (10.1%). The incidence of confirmed hypoglycemia in this study, defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤50 mg/dL, was 2.4% and 0.8% for ONGLYZA 2.5 mg and ONGLYZA 5 mg and 0.7% for placebo. The incidence of reported hypoglycemia for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo given as monotherapy was 4.0% and 5.6% versus 4.1%, respectively, 7.8% and 5.8% versus 5% given as add-on therapy to metformin, and 4.1% and 2.7% versus 3.8% given as add-on therapy to TZD. The incidence of reported hypoglycemia was 3.4% in treatment-naive patients given ONGLYZA 5 mg plus metformin and 4.0% in patients given metformin alone.

Hypersensitivity Reactions

Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. None of these events in patients who received ONGLYZA required hospitalization or were reported as life-threatening by the investigators. One saxagliptin-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Vital Signs

No clinically meaningful changes in vital signs have been observed in patients treated with ONGLYZA.

Laboratory Tests

Absolute Lymphocyte Counts

There was a dose-related mean decrease in absolute lymphocyte count observed with ONGLYZA. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microL, mean decreases of approximately 100 and 120 cells/microL with ONGLYZA 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when ONGLYZA 5 mg was given in initial combination with metformin compared to metformin alone. There was no difference observed for ONGLYZA 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count <750 cells/microL was 0.5%, 1.5%, 1.4%, and 0.4% in the saxagliptin 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to ONGLYZA although some patients had recurrent decreases upon rechallenge that led to discontinuation of ONGLYZA. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of ONGLYZA on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

Platelets

ONGLYZA did not demonstrate a clinically meaningful or consistent effect on platelet count in the six, double-blind, controlled clinical safety and efficacy trials.

DRUG INTERACTIONS

Inducers of CYP3A4/5 Enzymes

Rifampin significantly decreased saxagliptin exposure with no change in the area under the time-concentration curve (AUC) of its active metabolite, 5-hydroxy saxagliptin. The plasma dipeptidyl peptidase-4 (DPP4) activity inhibition over a 24-hour dose interval was not affected by rifampin. Therefore, dosage adjustment of ONGLYZA is not recommended. [See *Clinical Pharmacology* (12.3).]

Inhibitors of CYP3A4/5 Enzymes

Moderate Inhibitors of CYP3A4/5

Diltiazem increased the exposure of saxagliptin. Similar increases in plasma concentrations of saxagliptin are anticipated in the presence of other moderate CYP3A4/5 inhibitors (e.g., amprenavir, aprepitant, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil); however, dosage adjustment of ONGLYZA is not recommended. [See *Clinical Pharmacology* (12.3).]

Strong Inhibitors of CYP3A4/5

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor. [See *Dosage and Administration* (2.3) and *Clinical Pharmacology* (12.3).]

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA (saxagliptin), like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the maximum recommended human dose (MRHD) of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD. When administered to rats in combination with metformin, saxagliptin was not teratogenic nor embryolethal at exposures 21 times the saxagliptin MRHD. Combination administration of metformin with a higher dose of saxagliptin (109 times the saxagliptin MRHD) was associated with craniorachischisis (a rare neural tube defect characterized by incomplete closure of the skull and spinal column) in two fetuses from a single dam. Metformin exposures in each combination were 4 times the human exposure of 2000 mg daily.

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

Nursing Mothers

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ONGLYZA in pediatric patients have not been established.

Geriatric Use

In the six, double-blind, controlled clinical safety and efficacy trials of ONGLYZA, 634 (15.3%) of the 4148 randomized patients were 65 years and over, and 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients ≥65 years old and the younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Saxagliptin and its active metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. [See *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.3).]

OVERDOSAGE

In a controlled clinical trial, once-daily, orally-administered ONGLYZA in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

Instructions

Patients should be informed of the potential risks and benefits of ONGLYZA and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Physicians should instruct their patients to read the Patient Package Insert before starting ONGLYZA therapy and to reread it each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom or if any existing symptom persists or worsens.

Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C, with a goal of decreasing these levels toward the normal range. A1C is especially useful for evaluating long-term glycemic control. Patients should be informed of the potential need to adjust their dose based on changes in renal function tests over time.

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