

Immunoglobulin Test May Signal Cancer Risk

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Senior Editor

ATLANTA — Healthy blood donors with positive direct antiglobulin tests develop cancer more than twice as often as those who test negative, according to a provocative study that linked thousands of blood bank records to Israel's national cancer registry.

Absolute cancer risk was small in the study: Of people with positive direct

antiglobulin tests (DATs), 2.9% developed cancer, compared with 1.2% of DAT-negative donors, Dr. Ora Paltiel reported in a poster at the annual meeting of the American Society of Hematology.

Relative cancer risk was high, however, with hazard ratios of 2.46 overall, 14.20 for hematopoietic cancers, and 8.02 for lymphomas. Even when the investigators excluded cases diagnosed within 12 months of blood donation, people with positive DAT tests had an eightfold higher risk of

developing a hematopoietic cancer at an average follow-up of 66 months.

"In a small minority of people, a positive DAT is actually a marker—not a risk factor, a marker—that they have some cancer growing," said Dr. Paltiel, a hematologist and epidemiologist at the Hadassah University Medical Center, Jerusalem.

"Practically, you would not want to bring a panic because of this, but there are implications to a positive DAT," she said, urging additional studies to confirm the

finding and determine whether DAT testing could help detect early cancers in healthy people.

The DAT test (also known as a direct Coombs' test) has been used since the 1950s to see whether the donor has immunoglobulin antibodies attached to red blood cells, according to Dr. Paltiel. It is not universally required of blood donors, but a positive finding can suggest an immune reaction to a disease process.

The investigators identified 586 blood donors who had positive DAT screens during the years 1993-2003, and matched them by gender, age, and year of blood donation to 2,344 DAT-negative donors. Using unique identification numbers, the study was able to determine cancer incidence through July 30, 2006, in both cohorts. Men made up 63% of the population. The DAT-positive donors were slightly older (34.5 years vs. 32 years on average).

All told, 17 DAT-positive donors and 27 DAT-negative donors developed cancer by mid-2006. Dr. Paltiel said that DAT-positive patients tended to be diagnosed with

SymLin® (pramlintide acetate) injection

SymLinPen™ (pramlintide acetate) pen-injector

SymLin Brief Summary: For complete details, please see Prescribing Information.

WARNING
SymLin is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe hypoglycemia associated with SYMLIN use occurs, it is seen within 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.

INDICATIONS AND USAGE

SymLin is given at mealtimes and is indicated for:

- Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.
- Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.

CONTRAINDICATIONS

SymLin is contraindicated in patients with any of the following:

- a known hypersensitivity to SYMLIN or any of its components, including metacresol;
- a confirmed diagnosis of gastroparesis;
- hypoglycemia unawareness.

WARNINGS

Patient Selection

Proper patient selection is critical to safe and effective use of SYMLIN. Before initiation of therapy, the patient's HbA1c, recent blood glucose monitoring data, history of insulin-induced hypoglycemia, current insulin regimen, and body weight should be reviewed. SYMLIN therapy should only be considered in patients with insulin-using type 2 or type 1 diabetes who fulfill the following criteria:

- have failed to achieve adequate glycemic control despite individualized insulin management;
- are receiving ongoing care under the guidance of a healthcare professional skilled in the use of insulin and supported by the services of diabetes educator(s).

Patients meeting any of the following criteria should NOT be considered for SYMLIN therapy:

- poor compliance with current insulin regimen;
- poor compliance with prescribed self-blood glucose monitoring;
- have an HbA1c >9%;
- recurrent severe hypoglycemia requiring assistance during the past 6 months;
- presence of hypoglycemia unawareness;
- confirmed diagnosis of gastroparesis;
- require the use of drugs that stimulate gastrointestinal motility;
- pediatric patients.

Hypoglycemia. SYMLIN alone does not cause hypoglycemia. However, SYMLIN is indicated to be co-administered with insulin therapy and in this setting SYMLIN increases the risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes.

Severe hypoglycemia associated with SYMLIN occurs within the first 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Therefore, when introducing SYMLIN therapy, appropriate precautions need to be taken to avoid increasing the risk for insulin-induced severe hypoglycemia. These precautions include frequent pre- and post-meal glucose monitoring combined with an initial 50% reduction in pre-meal doses of short-acting insulin (see DOSAGE and ADMINISTRATION).

Symptoms of hypoglycemia may include hunger, headache, sweating, tremor, irritability, or difficulty concentrating. Rapid reductions in blood glucose concentrations may induce such symptoms regardless of glucose values. More severe symptoms of hypoglycemia include loss of consciousness, coma, or seizure.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes; diabetic nerve disease; use of medications such as beta-blockers, clonidine, guanethidine, or reserpine; or intensified diabetes control. The addition of any antihyperglycemic agent such as SYMLIN to an existing regimen of one or more anti-hyperglycemic agents (e.g., insulin, sulfonylurea), or other agents that can increase the risk of hypoglycemia may necessitate further insulin dose adjustments and particularly dose monitoring of blood glucose.

The following are examples of substances that may increase the blood glucose-lowering effect and susceptibility to hypoglycemia: oral anti-diabetic products, ACE inhibitors, diospyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates, and sulfonamide antibiotics.

Clinical studies employing a controlled hypoglycemic challenge have demonstrated that SYMLIN does not alter the counter-regulatory hormonal response to insulin-induced hypoglycemia. Likewise, in SYMLIN-treated patients, the perception of hypoglycemic symptoms was not altered with plasma glucose concentrations as low as 45 mg/dL.

PRECAUTIONS

General:

Hypoglycemia (See WARNINGS).

SymLin should be prescribed with caution to persons with visual or dexterity impairment.

Information for Patients: Healthcare providers should inform patients of the potential risks and advantages of SYMLIN therapy. Healthcare providers should also inform patients about self-management practices including glucose monitoring, proper injection technique, timing of dosing, and proper storage of SYMLIN. In addition, reinforce the importance of adherence to meal planning, physical activity, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. Refer patients to the SYMLIN Medication Guide and Patient Instructions for Use for additional information.

Instruct patients on handling of special situations such as intercurrent conditions (illness or stress), an inadequate or omitted insulin dose, inadvertent administration of increased insulin or SYMLIN dose, inadequate food intake or missed meals.

SymLin and insulin should always be administered as separate injections and never be mixed.

Women with diabetes should be advised to inform their healthcare professional if they are pregnant or contemplating pregnancy.

Renal Impairment: The dosing requirements for SYMLIN are not altered in patients with moderate or severe renal impairment ($Cl_{CR} >20$ to ≤ 50 mL/min). No studies have been done in dialysis patients.

Hepatic Impairment: Studies have not been performed in patients with hepatic impairment. However, hepatic dysfunction is not expected to affect blood concentrations of SYMLIN.

Allergy: Local allergy. Patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than SYMLIN, such as irritants in a skin cleansing agent or improper injection technique.

Systemic Allergy. In controlled clinical trials up to 12 months, potential systemic allergic reactions were reported in 65 (5%) of type 2 patients and 59 (5%) of type 1 SYMLIN-treated patients. Similar reactions were reported by 18 (4%) and 28 (5%) of placebo-treated type 2 and type 1 patients, respectively. No patient receiving SYMLIN was withdrawn from a trial due to a potential systemic allergic reaction.

Drug Interactions

Due to its effects on gastric emptying, SYMLIN therapy should not be considered for patients taking drugs that alter gastrointestinal motility (e.g., anticholinergic agents such as atropine) and agents that slow the intestinal absorption of nutrients (e.g., α -glucosidase inhibitors). Patients using these drugs have not been studied in clinical trials.

SymLin has the potential to delay the absorption of concomitantly administered oral medications. When the rapid onset of a concomitant orally administered agent is a critical determinant of effectiveness (such as analgesics), the agent should be administered at least 1 hour prior to or 2 hours after SYMLIN injection.

In clinical trials, the concomitant use of sulfonylureas or biguanides did not alter the adverse event profile of SYMLIN. No formal interaction studies have been performed to assess the effect of SYMLIN on the kinetics of oral antidiabetic agents.

Mixing SYMLIN and Insulin

The pharmacokinetic parameters of SYMLIN were altered when mixed with regular, NPH, and 70/30 premixed formulations of recombinant human insulin immediately prior to injection. **Thus, SYMLIN and insulin should not be mixed and must be administered separately.**

Pregnancy

Teratogenic Effects: Pregnancy Category C. No adequate and well-controlled studies have been conducted in pregnant women. Studies in perfused human placenta indicate that SYMLIN has low potential to cross the maternal/fetal placental barrier. Embryofetal toxicity studies with SYMLIN have been performed in rats and rabbits. Increases in congenital abnormalities (neural tube defect, cleft palate, exencephaly) were observed in fetuses of rats treated during organogenesis with 0.3 and 1.0 mg/kg/day (10 and 47 times the exposure resulting from the maximum recommended human dose based on AUC, respectively). Administration of doses up to 0.3 mg/kg/day SYMLIN (9 times maximum recommended dose based on AUC) to pregnant rabbits had no adverse effects in embryofetal development; however, animal reproduction studies are not always predictive of human response. SYMLIN should be used during pregnancy only if it is determined by the healthcare professional that the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is unknown whether SYMLIN is excreted in human milk. Many drugs, including peptide drugs, are excreted in human milk. Therefore, SYMLIN should be administered to nursing women only if it is determined by the healthcare professional that the potential benefit outweighs the potential risk to the infant.

Pediatric Use

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

Geriatric Use

SymLin has been studied in patients ranging in age from 15 to 84 years of age, including 539 patients 65 years of age or older. The change in HbA1c values and hypoglycemia frequencies did not differ by age, but greater sensitivity in some older individuals cannot be ruled out. Thus, both SYMLIN and insulin regimens should be carefully managed to obviate an increased risk of severe hypoglycemia.

ADVERSE REACTIONS

Adverse events (excluding hypoglycemia, discussed below) commonly associated with SYMLIN when co-administered with a fixed dose of insulin in the long-term, placebo-controlled trials in insulin-using type 2 patients and type 1 patients, respectively, are presented in the following paragraphs. The same adverse events were also shown in the open-label clinical practice study, which employed flexible insulin dosing. These are also presented below.

Adverse events in patients with insulin-using type 2 diabetes.—Treatment-emergent adverse events occurring with $\geq 5\%$ incidence and greater incidence with SYMLIN (120 mcg) compared with placebo in long-term, placebo-controlled trials are shown for placebo + insulin (N=284), SYMLIN + insulin (N=292), and for the open-label clinical practice study of SYMLIN + insulin (N=166), respectively (n (%)): nausea 34 (12), 81 (28), 53 (30); headache 19 (7), 39 (13), 8 (5); anorexia 5 (2), 27 (9), 1 (<1); vomiting 12 (4), 24 (8), 13 (7); abdominal pain 19 (7), 23 (8), 3 (2); fatigue 11 (4), 20 (7), 5 (3); dizziness 11 (4), 17 (6), 3 (2); coughing 12 (4), 18 (6), 4 (2); pharyngitis 7 (2), 15 (5), 6 (3).

Adverse events in patients with type 1 diabetes.—Treatment-emergent adverse events occurring with $\geq 5\%$ incidence and greater incidence with SYMLIN (30 or 60 mcg) compared to placebo in long-term, placebo-controlled studies are shown for placebo + insulin (N=538), SYMLIN + insulin (N=716), and for the open-label clinical practice study of SYMLIN + insulin (N=265), respectively (n (%)): nausea 92 (17), 342 (48), 98 (37); anorexia 12 (2), 122 (17), 0 (0); inflamed injury 55 (10), 97 (14), 20 (8); vomiting 36 (7), 82 (11), 18 (7); arthralgia 27 (5), 51 (7), 6 (2); fatigue 22 (4), 51 (7), 12 (4.5); allergic reaction 28 (5), 41 (6), 1 (<1); dizziness 21 (4), 34 (5), 5 (2). Most adverse events were gastrointestinal in nature. In patients with type 2 or type 1 diabetes, the incidence of nausea was higher at the beginning of SYMLIN treatment and decreased with time in most patients. The incidence and severity of nausea are reduced when SYMLIN is gradually titrated to the recommended doses (see DOSAGE and ADMINISTRATION).

Severe Hypoglycemia

SymLin alone (without the concomitant administration of insulin) does not cause hypoglycemia. However, SYMLIN is indicated as an adjunct treatment in patients who use mealtime insulin therapy and co-administration of SYMLIN with insulin can increase the risk of insulin-induced hypoglycemia, particularly in patients with type 1 diabetes (see Boxed Warning). The incidence of severe hypoglycemia during the SYMLIN clinical development program is summarized in the following paragraphs.

Severe hypoglycemia in patients with insulin-using type 2 diabetes.—Incidence and event rate of severe hypoglycemia in long-term, placebo-controlled studies (no insulin dose-reduction during initiation) and in the open-label, clinical practice study (insulin dose-reduction during initiation) are as follows. In the long-term, placebo-controlled studies, the patient-ascertained* event rate (event rate/patient year) for placebo + insulin was 0.24 and 0.13, at 0-3 months (n=284) and at >3-6 months (n=251), respectively, and the patient-ascertained incidence was 2.1% and 2.4%, respectively; medically assisted** event rate (event rate/patient year) was 0.06 and 0.07, at 0-3 months and at >3-6 months, respectively, and the medically assisted incidence was 0.7% and 1.2%, respectively. Also in these studies, the patient-ascertained event rate (event rate/patient year) for SYMLIN + insulin was 0.45 and 0.39, at 0-3 months (n=292) and at >3-6 months (n=255), respectively, and the patient-ascertained incidence was 8.2% and 4.7%, respectively; medically assisted event rate (event rate/patient year) was 0.09 and 0.02, at 0-3 months and at >3-6 months, respectively, and the medically assisted incidence was 1.7% and 0.4%, respectively. In the open-label, clinical practice study of SYMLIN + insulin, the patient-ascertained event rate (event rate/patient year) was 0.05 and 0.03, at 0-3 months (n=166) and at >3-6 months (n=150), respectively, and the patient-ascertained incidence was 0.6% and 0.7%, respectively; medically assisted event rate (event rate/patient year) was 0.05 and 0.03, at 0-3 months and at >3-6 months, respectively, and the medically assisted incidence was 0.6% and 0.7%, respectively.

Severe hypoglycemia in patients with type 1 diabetes.—Incidence and event rate of severe hypoglycemia in long-term, placebo-controlled studies (no insulin dose-reduction during initiation) and in the open-label, clinical practice study (insulin dose-reduction during initiation) are as follows. In the long-term, placebo-controlled studies, the patient-ascertained* event rate (event rate/patient year) for placebo + insulin was 1.33 and 1.06, at 0-3 months (n=538) and at >3-6 months (n=470), respectively, and the patient-ascertained incidence was 10.8% and 8.7%, respectively; medically assisted** event rate (event rate/patient year) was 0.19 and 0.24, at 0-3 months and at >3-6 months, respectively, and the medically assisted incidence was 3.3% and 4.3%, respectively. Also in these studies, the patient-ascertained event rate (event rate/patient year) for SYMLIN + insulin was 1.55 and 0.82, at 0-3 months (n=716) and at >3-6 months (n=576), respectively, and the patient-ascertained incidence was 16.8% and 11.1%, respectively; medically assisted event rate (event rate/patient year) was 0.50 and 0.27, at 0-3 months and at >3-6 months, respectively, and the medically assisted incidence was 7.3% and 5.2%, respectively. In the open-label, clinical practice study of SYMLIN + insulin, the patient-ascertained event rate (event rate/patient year) was 0.29 and 0.16, at 0-3 months (n=265) and at >3-6 months (n=213), respectively, and the patient-ascertained incidence was 5.7% and 3.8%, respectively; medically assisted event rate (event rate/patient year) was 0.10 and 0.04, at 0-3 months and at >3-6 months, respectively, and the medically assisted incidence was 2.3% and 0.9%, respectively.

* **Patient-ascertained severe hypoglycemia:** Requiring the assistance of another individual (including aid in ingestion of oral carbohydrate); and/or requiring the administration of glucagon injection, intravenous glucose, or other medical intervention.

** **Medically assisted severe hypoglycemia:** Requiring glucagon, IV glucose, hospitalization, paramedic assistance, emergency room visit, and/or assessed as an SAE by the investigator.

OVERDOSAGE

Single 10 mg doses of SYMLIN (83 times the maximum dose of 120 mcg) were administered to three healthy volunteers. Severe nausea was reported in all three individuals and was associated with vomiting, diarrhea, vasodilatation, and dizziness. No hypoglycemia was reported. SYMLIN has a short half-life and in the case of overdose, supportive measures are indicated.

DOSAGE AND ADMINISTRATION

SymLin dosage differs depending on whether the patient has type 2 or type 1 diabetes (consult Prescribing Information for dosing instructions). When initiating therapy with SYMLIN, initial insulin dose reduction is required in all patients (both type 2 and type 1) to reduce the risk of insulin-induced hypoglycemia. As this reduction in insulin can lead to glucose elevations, patients should be monitored at regular intervals to assess SYMLIN tolerability and the effect on blood glucose, so that individualized insulin adjustments can be initiated. If SYMLIN therapy is discontinued for any reason (e.g., surgery or illnesses), the same initiation protocol should be followed when SYMLIN therapy is re-initiated.

The SymLinPen™ pen-injectors and SYMLIN vials are manufactured for: Amylin Pharmaceuticals, Inc., San Diego, CA 92121 USA 1-800-349-8919 <http://www.symlin.com>

Rx only

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'A positive DAT is actually a marker—not a risk factor, a marker—that they have some cancer growing.'

DR. PALTIEL

cancer earlier than those who were DAT negative, perhaps because they had a physical exam after receiving letters notifying them of the DAT results. Three DAT-positive donors were diagnosed with hematopoietic cancers (Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma) during the first year.

The investigators did a subset analysis excluding early diagnoses in people who may have had undiagnosed cancers at the time of blood donation. Looking just at DAT-positive donors diagnosed with cancers after 12 months, the most common malignancies (with two in each category) were lymphoma, multiple myeloma, and thyroid, prostate, and gastrointestinal tumors.

Comparisons of observed cases of cancer in blood donors with expected cases in the general population also found twice the incidence of cancer in DAT-positive donors, but no elevation of cancer rates in those who had tested DAT negative. Incidence of hematologic malignancies was 11-fold higher in the DAT-positive donors, according to the poster. This reflected somewhat increased rates of lymphomas and Hodgkin's lymphoma and a more than 40-fold hike in incidence of multiple myeloma, compared with expected rates.

The increase in a condition as rare as multiple myeloma cannot simply be attributed to more people being screened after a positive DAT test, Dr. Paltiel said. "Some of it has to do with health behavior, but you can't blame myeloma on health behavior." If a positive DAT leads to earlier diagnosis, she added, the person could benefit from recent advances in treatment of multiple myeloma. ■