Eosinophilic Esophagitis Diagnoses Rising Fast

BY KATE JOHNSON

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MONTREAL — The incidence of adult and pediatric eosinophilic esophagitis appears to be increasing dramatically, and endoscopic investigation and treatment have low complication rates, according to the findings of the largest reported population-based study of the disorder.

Dr. Chad Williams and his colleagues from the University of Calgary (Alta.)

found an incidence of 7.2 cases/100,000 person-years in 2006 in the Calgary Health Region (population 1.2 million), the highest incidence to date, they reported in a poster at the Canadian Digestive Diseases

'The number of diagnoses per year is definitely rising," Dr. Williams said in an interview. "Whether that reflects a true increase in incidence we're not sure. We may be just recognizing it more."

Few studies have investigated the inci-

dence of eosinophilic esophagitis in general, and none has addressed the incidence in the adult North American population in particular, he said. A European study reported an adult incidence of 6 cases/100,000 person-years (J. Allergy Clin. Immunol. 2005;115:418-9).

In their retrospective cohort study, Dr. Williams and his colleagues identified adult and pediatric biopsy-proven cases of eosinophilic esophagitis in the Calgary Health Region between 2002 and 2006.

Overall, there were two cases identified in 2002, and no cases in 2003. However, the reported incidence rose dramatically from 1.83 cases/100,000 person-years in 2004 to 4.27 cases in 2005 and to 7.2 cas-

The incidence per 1,000 upper endoscopies rose from 2.16 cases in 2004 to 8.35

The incidence seemed to increase in adults, while it dipped among children. The number of cases in adults went from 5 in 2004 to 75 in 2006, compared with 16 in 2004 to 6 in 2006 in children.

Among the total of 158 identified cases, 75% of them were adults and 84% were male. The median age of adult patients was 39 years, and the median pediatric age was 12 years.

"In the pediatric population, patients usually present with food aversion, gastroesophageal refluxlike symptoms and abdominal pain, but in the adult popula-



Eosinophilic esophagitis (shown on endoscopy) is being detected more often.

tion, the two main symptoms are dysphagia and food bolus impaction," Dr. Williams explained at the conference, which was sponsored by the Canadian Association of Gastroenterology.

In a subanalysis of 144 of the eosinophilic esophagitis cases, the mean age of the patient population was 40 years (range 16-78 years), Dr. Williams' group reported in another poster.

Most (85%) of the patients were male; 74% presented with dysphagia and 18% with food impaction. Allergies were noted in 27% of patients, asthma in 22%, gastroesophageal reflux disease in about 20%, and autoimmune disease in about 3%. All of the patients underwent endoscopic evaluation and biopsy, with 22% of patients also receiving concurrent therapeutic esophageal dilation.

Endoscopic complications were more common in patients undergoing dilation, with six mucosal tears documented, but no perforations, Dr. Williams said.

In patients undergoing endoscopic biopsy alone, there was one mucosal tear resulting from the biopsy, and one resulting from trauma from the endoscope. Dr. Williams noted that overall this complication rate was low, compared with a previously reported rate of 30% (Clin. Gastroenterol. Hepatol. 2007;5:1149-53).

"Gastroscopy is a fairly safe procedure, although we did have one mucosal tear in our group, but I am not a proponent of dilation in this population," Dr. Williams said, adding that he recommends medical treatment with fluticasone as the first-line

References: 1. Brange J, Vølund A. Insulin analogs with improved pharmacokinetic profiles. Adv Drug Deliv Rev. 1999;35(2-3):307-335. 2. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care*. 2000;23(5):583-588. **3**. Korytkowski M, Bell D, Jacobsen C, Suwannasari R, for the FlexPen® Study Team. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. *Clin Ther*. 2003;25(11):2836-2848. **4**. Niskanen L, Jensen LE, Råstam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. Clin Ther. 2004;26(4):531-540.



BRIEF SUMMARY. PLEASE CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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NovoLog is indicated for the treatment of patients with diabetes mellitus, for the control of hyperglycemia. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, NovoLog given by injection should normally be used in regimens with an intermediate or long-acting insulin. NovoLog may also be infused subcutaneously by external insulin pumps. NovoLog may be administered intravenously under proper medical supervision in a clinical setting for glycemic control. (See WARNINGS; PRECAUTIONS [especially Usage in Pumps], Mixing of Insulins.)

NovoLog is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog or one of its excipients.

WARNINGS
NovoLog differs from regular human insulin by a more rapid on and a shorter duration of activity. Because of the fast onset of action, the injection of NovoLog should immediately be followe by a meal. Because of the short duration of action of NovoLog, patients with diabetes also require a longer-acting insulin to maintain adequate glucose control. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy.

important for patients using external pump infusion therapy.
Hypoglycemia is the most common adverse effect of insulin
therapy, including Novolog, As with all insulins, the timing of
hypoglycemia may differ among various insulin formulations.
Any change of insulin dose should be made cautiously and only
under medical supervision. Changes in insulin strength,
manufacturer, type (e.g., regular, NPH, analog), species (animal,
human), or method of manufacture (PDNA versus animal-source
insulin Pumps: When used in an external insulin pump for
subcutaneous infusion, Novolog should not be diluted or mixed
with any other insulin. Physicians and patients should carefully
evaluate information on pump use in the Novolog physician and
patient package inserts and in the pump manufacturer's manual
(e.g., Novolog-specific information should be followed for in-use
time, frequency of changing infusion sets, or other details specific
to Novolog usage, because Novolog-specific information may
differ from general pump manual instructions).
Pump or infusion set malfunctions or insulin degradation can lead

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Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have shorter duration of action. These differences may be particularly relevant when patients are switched from multiple injection therapy or infusion with buffered regular insulin. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required. (See PRECAUTIONS, Mixing of Insulins.)

Mixing of Insulins.)

PRECAUTIONS

General

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of Novolog and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium-level). Insulin stimulates potassium movement into the cells, possibly leading to hypokalemia that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Since intravenously administered insulin has a rapid onset of action, increased attention to hypoglycemia and hypokalemia is necessary. Therefore, glucose and potassium levels must be monitored closely when Novolog or any other insulin's administered intravenously, the Novolog or any other insulin's administered intravenously, the other properties of the properties of hypoglycemic reactions may be associated with the administration of Novolog. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia (and, possibly, loss of

Systemic Allergy - Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening.

In controlled clinical trials using injection therapy, allergic reactions were reported in 3 of 735 patients (0.4%) who received regular human insulin and 10 of 1394 patients (0.7%) who received NovoLog. During these and other trials, 3 of 2341 patients treated with NovoLog were discontinued due to allergic reactions.

Antibody Production - Increases in levels of anti-insulin antibodies that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog. The number of patients treated with insulin aspart experiencing these increases is greater than the number among those treated with human regular insulin. Data from a 12-month controlled trial in patients with Type 1 diabetes suggest that the increase in these antibodies is transient. The differences in antibody levels between the human regular insulin and insulin aspart treatment groups observed at 3 and 6 months were no longer evident at 12 months. The clinical significance of these antibodies is not known. They do not appear to cause deterioration in HbA1c or to necessitate increases in insulin dose.

Pregnancy and Lactation - Female patients should be advised to tell their physician if they intend to become, or if they become pregnant. Information is not available on the use of NovoLog during lactation (see PREGNANCY-TERATOGENIC EFFECTS-PREGNANCY CATEGORY).

Usage in Pumps - NovoLog is recommended for use in pump systems suitable for insulin infusion as listed below.

Pumps: Disetronic H-TRON® series, MiniMed 500 series and other equivalent pumps.

Reservoirs and Infusion Sets: NovoLog is recommended for use in any creactions. Indv Production - Increases in levels of anti-insulin antibodies that react

equivalent pumps.

Reservoirs and Infusion Sets: NovoLog is recommended for use in any reservoir and infusion sets that are compatible with insulin and the specific pump. In-vitro studies have shown that pump malfunction, loss of cresol, and insulin degradation may occur when NovoLog is maintained in a pump system for more than 48 hours. Reservoirs and infusion sets should be changed at least every 48 hours.

PRECAUTIONS, Mixing or Insulins).

Laboratory Tests

As with all insulin therapy, the therapeutic response to NovoLog should be monitored by periodic blood glucose tests. Periodic measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control. When NovoLog is administered intravenously, glucose and potassium levels must be closely monitored to avoid potentially fatal hypoglycemia and hypokalemia.

- he adjustment and particularly tools in initiating. The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.
- (e.g., octreotide), sulfonamide antibiotics. The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).
- estrogens, progestogens (e.g., in oral contraceptives). Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

- hypoglycemia may be reduced or asseru.

 Mixing of Insulins

 A clinical study in healthy male volunteers (n=24) demonstrated that mixing NovoLog with NPH human insulin immediately before injection produced some attenuation in the peak concentration of NovoLog, but that the time to peak and the total bioavailability of NovoLog were not significantly affected. If NovoLog is mixed with NPH human insulin, NovoLog should be drawn into the syringe first. The injection should be made immediately after mixing. Because there are no data on the compatibility of NovoLog and crystalline zinc insulin preparations, NovoLog should not be mixed with these preparations.

 The effects of mixing NovoLog with insulins of animal source or insulin preparations produced by other manufacturers have not been studied (see MARNINGS).
- Mixtures should not be administered intravenously.
- When used in external subcutaneous infusion pumps for insulin, NovoLog should not be mixed with any other insulins or diluent.

Carcinogenicity, Mutagenicity, Impairment of Fertility

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Standard 2-year carcinogenicity studies in animals have not been performed
to evaluate the carcinogenic potential of NovoLog. In 52-week studies,
Sprague-Dawley rats were dosed subcutaneously with NovoLog at 10, 50,
and 200 U/kg/day (approximately 2, 8, and 32 times the human
subcutaneous dose of 1.0 U/kg/day, DavoLog increased the incidence of
mammary gland tumors in females when compared to untreated controls.
The incidence of mammary tumors for NovoLog was not significantly different
than for regular human insulin. The relevance of these findings to humans is
not known. NovoLog was not genotoxic in the following tests: Ames test,
mouse lymphoma cell forward gene mutation test, human peripheral blood
lymphocyte chromosome aberration test, in vivo micronucleus test in mice,
and in ex vivo UDS test in rat liver hepatocytes. In fertility studies in male and
female rats, at subcutaneous doses up to 200 U/kg/day (approximately
32 times the human subcutaneous dose, based on U/body surface area),
no direct adverse effects on male and female fertility, or general reproductive
performance of animals was observed.

Pregnancy - Teratogenic Effects - Pregnancy Category B

Pregnancy - Teratogenic Effects - Pregnancy Category B All pregnancies have a background risk of birth defects, loss, or o

All pregnances have a dataglound risk of only release, so, of other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of

and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients

in such patients.

An open-label, randomized study compared the safety and efficacy of NovoLog versus human insulin in the treatment of pregnant women with Type 1 diabetes (322 exposed pregnancies (NovoLog: 157, human insulin: 165)). Two-thirds of the enrolled patients were already pregnant when they entered the study. Since only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Mean HbA1 c of ~69% was observed in both groups during pregnancy, and there was no significant difference in the incidence of maternal hypoglycemia.

maternal hypoglycemia. Subcutaneous reproduction and teratology studies have been performed with Novolog and regular human insulin in rats and rabbits. In these studies, Novolog was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of Novolog did not differ from those observed with subcutaneous regular human insulin. Novolog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for abbits, based on U/body surface area.

Nursing Mothers

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It is unknown whether insulin aspart is excreted in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when NovoLog is administered to a nursing mother.

Pediatric Use
A 24-week, parallel-group study of children and adolescents with Type 1
diabetes (n=283) age 6 to 18 years compared the following treatment
regimens: NovoLog (n=187) or Novolin R (n=96). NPH insulin was
administered as the basal insulin. NovoLog achieved glycemic control
comparable to Novolin R, as measured by change in Hah 1c. The incidence of
hypoglycemia was similar for both treatment groups. NovoLog and regular
human insulin have also been compared in children with Type 1 diabetes
(n=26) age 2 to 6 years. As measured by end-of-treatment HbA1c and
fructosamine, glycemic control with NovoLog was comparable to that
obtained with regular human insulin. As observed in the 6 to 18 year old
pediatric population, the rates of hypoglycemia were similar in both
treatment groups.

treatment groups.

Geriatric Use

Of the total number of patients (n=1,375) treated with NovoLog in 3 human insulin-controlled clinical studies, 2.6% (n=36) were 65 years of age or over. Half of these patients had Type 1 diabetes (18/1285) and half had Type 2 (18/90) diabetes. The HbA1 c response to NovoLog, as compared to human insulin, did not differ by age, particularly in patients with Type 2 diabetes. Additional studies in larger populations of patients 65 years of age or over are needed to permit conclusions regarding the safety of NovoLog in elderly compared to younger patients. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of NovoLog action have not been performed.

Clinical trials comparing NovoLog with regular human insulin did not demonstrate a difference in frequency of adverse events between the

Body as Whole - Allergic reactions (see PRECAUTIONS, Allergy).

Skin and Appendages - Injection site reaction, lipodystrophy, pruritus, rash (see PRECAUTIONS, Allergy, Usage in Pumps).

Other - Hypoglycemia, hyperglycemia and ketosis (see WARNINGS and PRECAUTIONS). In controlled clinical trials, small, but persistent elevations in alkaline phosphatase result were observed in some patients treated with NovoLog. The clinical significance of this finding is unknown.

OVERDOSAGE
Excess insulin may cause hypoglycemia and hypokalemia, particularly during IV administration. Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with roal glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, sezure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbothydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

More detailed information is available on request.

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