

BI-RADS 3 Category Assessment Holds Up

VITALS

Major Finding: When breast lesions were assessed with MRI and placed in the BI-RADS category 3, a total of 162 lesions were benign and 5 were malignant on follow-up.

Data Source: A prospective study of 473 women.

Disclosures: Dr. O'Loughlin disclosed no conflicts of interest. The study was funded by an unrestricted grant from the Connecticut Breast Health Initiative.

BY PATRICE WENDLING

CHICAGO — The majority of breast lesions assessed with magnetic resonance imaging and placed in the BI-RADS category 3 were benign on follow-up in a prospective study of 473 women.

The finding is reassuring because the category is reserved for “probably benign” findings, but doesn't

resolve the confusion that exists over how to manage these lesions, according to lead researcher Dr. Michael T. O'Loughlin.

The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) breast lexicon was created in 2003 to standardize breast mammography, ultrasound, and MRI reporting. It includes assessment categories similar to

those used in mammography, but doesn't tell physicians when to follow up on category 3 lesions. This had led some insurance companies to balk at providing coverage of follow-up breast MRIs in less than 1 year from the original study and some physicians to proceed directly to biopsy, he explained at the annual meeting of the Radiological Society of North America.

Dr. O'Loughlin and his colleagues scanned 473 women, with 158 (33%) given either a unilateral (104 women) or bilateral (54 women) category 3 assessment on their initial study. The lesions included 126 foci of enhancement, 65 non-masslike regions of enhancement, and 35 benign-appearing masses, likely lymph nodes or fibroadenomas. A total of 119 women (75%) returned for follow-up imaging at a mean of 278 days after the initial examination (range, 31-951 days).

On follow-up, 162 lesions were benign and 5 were malignant, said Dr. O'Loughlin, a radiologist in a group practice in Hartford, Conn.

For the five cancers, the final diagnosis was confirmed on average 129 days after the initial MRI exam (range, 3-210 days). They consisted of one ductal carcinoma in situ and four invasive carcinomas, and ranged in size from 3 mm to 8 mm. All patients were node negative.

Session moderator Dr. Elizabeth Morris, director of breast MRI and breast imaging at Memorial Sloan-Kettering Cancer Center in New York, asked Dr. O'Loughlin how he handles follow-up in these patients, remarking that the average time for cancer change seems to be about 4 months.

“I like 6 months,” he responded. “If it is cancer on follow-up, at most it is a 6-month delay. If I know the patient will not be returning for a year, I'd be calling it category 3 much less.”

Confusion over the follow-up of category 3 lesions on breast MRI will be reduced with more studies looking at the outcome of this assessment category, Dr. O'Loughlin said in an interview.

“Thankfully the number of category 3 lesions that eventually are determined to be cancers is relatively rare,” he said in the interview. “This is great for patients, but makes meaningful outcome data difficult to obtain.”

Women given a category 3 assessment had a significantly lower mean age of 48.7 years, compared with 52 years for the remaining women. The MRI exams may not have been scheduled optimally for hormonally active breast tissue, which may help explain the younger age in women given the category 3 assessment, Dr. O'Loughlin said.

The mean age in the study was 50.9 years, and 91% of patients were white.

The majority of women were being scanned for diagnostic rather than screening purposes. Clinical indications included a new diagnosis of breast cancer (25%), a remote history of breast cancer (17%), an abnormal mammogram (34%), a strong family history of breast cancer (27%), prior breast surgery (26%), and an implant evaluation (0.6%). ■

HUMALOG®

INSULIN LISPRO INJECTION (rDNA ORIGIN)

BRIEF SUMMARY: Consult package insert for complete prescribing information.

INDICATIONS AND USAGE: Humalog is an insulin analog that is indicated in the treatment of patients with diabetes mellitus for the control of hyperglycemia. Humalog has a more rapid onset and a shorter duration of action than regular human insulin. Therefore, in patients with type 1 diabetes, Humalog should be used in regimens that include a longer-acting insulin. However, in patients with type 2 diabetes, Humalog may be used without a longer-acting insulin when used in combination therapy with sulfonylurea agents.

Humalog may be used in an external insulin pump, but should not be diluted or mixed with any other insulin when used in the pump. Humalog administration in insulin pumps has not been studied in patients with type 2 diabetes.

CONTRAINDICATIONS: Humalog is contraindicated during episodes of hypoglycemia and in patients sensitive to Humalog or any of its excipients.

WARNINGS: This human insulin analog differs from regular human insulin by its rapid onset of action as well as a shorter duration of activity. When used as a mealtime insulin, the dose of Humalog should be given within 15 minutes before or immediately after the meal. Because of the short duration of action of Humalog, patients with type 1 diabetes also require a longer-acting insulin to maintain glucose control (except when using an external insulin pump).

External Insulin Pumps: When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin. Patients should carefully read and follow the external insulin pump manufacturer's instructions and the “PATIENT INFORMATION” leaflet before using Humalog.

Physicians should carefully evaluate information on external insulin pump use in the Humalog physician package insert and in the external insulin pump manufacturer's instructions. If unexplained hypoglycemia or ketosis occurs during external insulin pump use, prompt identification and correction of the cause is necessary. The patient may require interim therapy with subcutaneous insulin injections (see PRECAUTIONS, For Patients Using External Insulin Pumps, and DOSAGE AND ADMINISTRATION).

Hypoglycemia is the most common adverse effect associated with the use of insulins, including Humalog. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using an external insulin pump.

Any change in insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (eg, regular, NPH, analog), species, or method of manufacture may result in the need for a change in dosage.

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 Humalog and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (eg, patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level). Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of Humalog action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stress.

Hypoglycemia—As with all insulin preparations, hypoglycemic reactions may be associated with the administration of Humalog. Rapid changes in serum glucose concentrations 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 long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal Impairment—The requirements for insula may be reduced in patients with renal impairment.

Hepatic Impairment—Although impaired hepatic function does not affect the absorption or disposition of Humalog, careful glucose monitoring and dose adjustments of insulin, including Humalog, may be necessary.

Allergy—Local Allergy—As with any insulin therapy, 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 insulin, such as irritants in a skin cleansing agent or poor injection technique.

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. Localized reactions and generalized rhytias have been reported with the use of cresol as an injectable excipient. In Humalog-controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving Humulin R® (N=2969) and 30 patients receiving Humalog (N=2944) (P=.053).

Antibody Production—In large clinical trials, antibodies that cross-react with human insulin and insulin lispro were observed in both Humulin R- and Humalog-treatment groups. As expected, the largest increase in the antibody levels during the 12-month clinical trials was observed with patients new to insulin therapy.

Usage of Humalog in External Insulin Pumps—The infusion set (reservoir syringe, tubing, and catheter), Disetronic® D-TRON®2.3 or D-TRONplus®2.3 cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced and a new infusion site selected every 48 hours or less. Humalog in the external insulin pump should not be exposed to temperatures above 37°C (98.6°F).

In the D-TRON®2.3 or D-TRONplus®2.3 pump, Humalog 3 mL cartridges may be used for up to 7 days. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion site should be selected every 48 hours or less.

When used in an external insulin pump, Humalog should not be diluted or mixed with any other insulin (see INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, For Patients Using External Insulin Pumps, Mixing of Insulins, DOSAGE AND ADMINISTRATION, and Storage).

Information for Patients—Patients should be informed of the potential risks and advantages of Humalog and alternative therapies. Patients should also be informed about the importance of proper insulin storage, injection technique, timing of dosage, adherence to meal planning, regular physical activity, regular blood glucose monitoring, periodic hemoglobin A1C testing, recognition and management of hypoglycemia and hyperglycemia, and periodic assessment for diabetes complications.

Patients should be advised to inform their physician if they are pregnant or intend to become pregnant. Refer patients to the “PATIENT INFORMATION” leaflet for timing of Humalog dosing (≤15 minutes before or immediately after a meal), storing insulin, and common adverse effects.

For Patients Using Insulin Pen Delivery Devices: Before starting therapy, patients should read the “PATIENT INFORMATION” leaflet that accompanies the drug product and the User Manual that accompanies the delivery device. They should also read these materials each time the prescription is renewed. Patients should be instructed on how to properly use the delivery device, prime the Pen to a stream of insulin, and properly dispose of needles. Patients should be advised not to share their Pens with others.

For Patients Using External Insulin Pumps: Patients using an external infusion pump should be trained in intensive insulin therapy and in the function of their external insulin pump and pump accessories. Humalog was tested in the MiniMed® Models 506, 507, and 508 insulin pumps using MiniMed® Polyfin® infusion sets. Humalog was also tested in the Disetronic® H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir), and the Disetronic D-TRON®2.3 and D-TRONplus®2.3 insulin pumps (with Humalog 3 mL cartridges) using Disetronic Rapid® infusion sets.

The infusion set (reservoir syringe, tubing, catheter), D-TRON®2.3 or D-TRONplus®2.3 cartridge adapter, and Humalog in the external insulin pump reservoir should be replaced, and a new infusion site selected every 48 hours or less. Humalog in the external pump should not be exposed to temperatures above 37°C (98.6°F).

A Humalog 3 mL cartridge used in the D-TRON®2.3 or D-TRONplus®2.3 pump should be discarded after 7 days, even if it still contains Humalog. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected.

Laboratory Tests—As with all insulins, the therapeutic response to Humalog should be monitored by periodic blood glucose tests. Periodic measurement of hemoglobin A1C is recommended for the monitoring of long-term glycemic control.

Drug Interactions—Insulin requirements may be increased by medications with hyperglycemic activity, such as corticosteroids, isoniazid, certain lipid-lowering drugs (eg, niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy (see CLINICAL PHARMACOLOGY).

Insulin requirements may be decreased in the presence of drugs that increase insulin sensitivity or have hypoglycemic activity, such as oral antidiabetic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of pancreatic function (eg, octreotide), and alcohol. Beta-adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

Mixing of Insulins—Care should be taken when mixing all insulins as a change in peak action may occur. The American Diabetes Association warns in its Position Statement on Insulin Administration, “On mixing, physicochemical changes in the mixture may occur (either immediately or over time). As a result, the physiological response to the insulin mixture may differ from that of the injection of the insulins separately.” Mixing Humalog with Humulin® N or Humulin® U does not decrease the absorption rate or the total bioavailability of Humalog.

Given alone or mixed with Humulin N, Humalog results in a more rapid absorption and glucose-lowering effect compared with regular human insulin.

Pregnancy—Teratogenic Effects—Pregnancy Category B—Reproduction studies with insulin lispro have been performed in pregnant rats and rabbits at parenteral doses up to 4 and 0.3 times, respectively, the average human dose (40 units/day) based on body surface area. The results have revealed no evidence of impaired fertility or harm to the fetus due to Humalog. There are, however, no adequate and well-controlled studies with Humalog in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Although there are limited clinical studies of the use of Humalog in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Nursing Mothers—It is unknown whether Humalog is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when Humalog is administered to a nursing woman. Patients with diabetes who are lactating may require adjustments in Humalog dose, meal plan, or both.

Pediatric Use—In a 9-month, crossover study of prepubescent children (n=60), aged 3 to 11 years, comparable glycemic control as measured by A1C was achieved regardless of treatment group: regular human insulin 30 minutes before meals 8.4%, Humalog immediately before meals 8.4%, and Humalog immediately after meals 8.5%. In an 8-month, crossover study of adolescents (n=463), aged 9 to 19 years, comparable glycemic control as measured by A1C was achieved regardless of treatment group: regular human insulin 30 to 45 minutes before meals 8.7% and Humalog immediately before meals 8.7%. The incidence of hypoglycemia was similar for all 3 treatment regimens. Adjustment of basal insulin may be required. To improve accuracy in dosing in pediatric patients, a diluent may be used. If the diluent is added directly to the Humalog vial, the shelf life may be reduced (see DOSAGE AND ADMINISTRATION).

Geriatric Use—Of the total number of subjects (n=2834) in 8 clinical studies of Humalog, 12% (n=338) were 65 years of age or over. The majority of these were patients with type 2 diabetes. A1C values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of Humalog action have not been performed.

ADVERSE REACTIONS: Clinical studies comparing Humalog with regular human insulin did not demonstrate a difference in frequency of adverse events between the 2 treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as a Whole—allergic reactions (see PRECAUTIONS).

Skin and Appendages—injection site reaction, lipodystrophy, pruritus, rash.

Other—hypoglycemia (see WARNINGS and PRECAUTIONS).

OVERDOSAGE: 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 oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION: Humalog is intended for subcutaneous administration, including use in select external insulin pumps (see DOSAGE AND ADMINISTRATION, External Insulin Pumps). Dosage regimens of Humalog will vary among patients and should be determined by the healthcare provider familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. Pharmacokinetic and pharmacodynamic studies showed Humalog to be equipotent to regular human insulin (ie, one unit of Humalog has the same glucose-lowering effect as one unit of regular human insulin), but with more rapid activity. The quicker glucose-lowering effect of Humalog is related to the more rapid absorption rate from subcutaneous tissue. An adjustment of dose or schedule of basal insulin may be needed when a patient changes from other insulins to Humalog, particularly to prevent pruritic hyperglycemia.

When used as a mealtime insulin, Humalog should be given within 15 minutes before or immediately after a meal. Regular human insulin is best given 30 to 60 minutes before a meal. To achieve optimal glucose control, the amount of longer-acting insulin being given may need to be adjusted when using Humalog.

The rate of insulin absorption and consequently the onset of activity are known to be affected by the site of injection, exercise, and other variables. Humalog was absorbed at a consistently faster rate than regular human insulin in healthy male volunteers given 0.2 U/kg regular human insulin or Humalog at abdominal, deltoid, or femoral sites, the 3 sites often used by patients with diabetes. When not mixed in the same syringe with other insulins, Humalog maintains its rapid onset of action and has less variability in its onset of action among injection sites compared with regular human insulin (see PRECAUTIONS). After abdominal administration, Humalog concentrations are higher than those following deltoid or thigh injections. Also, the duration of action of Humalog is slightly shorter following abdominal injection, compared with deltoid and femoral injections. As with all insulin preparations, the time course of action of Humalog may vary considerably in different individuals or within the same individual. Patients must be educated to use proper injection techniques.

Humalog in a vial may be diluted with STERILE DILUENT for Humalog, Humulin N, Humulin R, Humulin 70/30, and Humulin® R U-500 to a concentration of 1:10 (equivalent to U-10) or 1:2 (equivalent to U-50). Diluted Humalog may remain in patient use for 28 days when stored at 5°C (41°F) and for 14 days when stored at 30°C (86°F). Do not dilute Humalog contained in a cartridge or Humalog used in an external insulin pump. Parenteral drug products should be inspected visually before use whenever the solution and the container permit. If the solution is cloudy, contains particulate matter, is thickened, or is discolored, the contents must not be injected. Humalog should not be used after its expiration date. The cartridge containing Humalog is not designed to allow any other insulin to be mixed in the cartridge or for the cartridge to be refilled with insulin.

External Insulin Pumps—Humalog was tested in MiniMed® Models 506, 507, and 508 insulin pumps using MiniMed® Polyfin® infusion sets. Humalog was also tested in the Disetronic® H-TRONplus® V100 insulin pump (with plastic 3.15 mL insulin reservoir) and the Disetronic D-TRON®2.3 and D-TRONplus®2.3 pumps (with Humalog 3 mL cartridges) using Disetronic Rapid® infusion sets. Humalog should not be diluted or mixed with any other insulin when used in an external insulin pump.

HOW SUPPLIED: Humalog (insulin lispro injection, USP [rDNA origin]) is available in the following package sizes (with each presentation containing 100 units insulin lispro per mL [U-100]):

10 mL vials	NDC 0002-7510-01	(VL-7510)
3 mL vials	NDC 0002-7510-17	(VL-7533)
5 x 3 mL cartridges ³	NDC 0002-7516-59	(VL-7516)
5 x 3 mL prefilled insulin delivery devices (Pen)	NDC 0002-8725-59	(HP-8725)
5 x 3 mL prefilled insulin delivery devices (Humalog® KwikPen™)	NDC 0002-8799-59	(HP-8799)

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³3 mL cartridge is for use in Eli Lilly and Company's HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3 mL insulin delivery device, and Disetronic D-TRON® and D-TRONplus® pumps. Autopen® is a registered trademark of Owen Mumford, Ltd. HumaPen®, HumaPen® MEMOIR™ and HumaPen® LUXURA™ HD are trademarks of Eli Lilly and Company. Other product and company names may be the trademarks of their respective owners.

Storage—Unopened Humalog should be stored in a refrigerator (2° to 8°C [36° to 46°F]), but not in the freezer. Do not use Humalog if it has been frozen. Unrefrigerated (below 30°C [86°F]) 12 vials, cartridges, Pens, and KwikPens must be used within 28 days or be discarded, even if they still contain Humalog. Protect from direct heat and light.

Use in an External Insulin Pump—A Humalog 3mL cartridge used in the D-TRON®2.3 or D-TRONplus®2.3 should be discarded after 7 days, even if it still contains Humalog. Infusion sets, D-TRON®2.3 and D-TRONplus®2.3 cartridge adapters, and Humalog in the external insulin pump reservoir should be discarded every 48 hours or less.

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KwikPens manufactured by Eli Lilly and Company, Indianapolis, IN 46285, USA.

Pens manufactured by Eli Lilly and Company, Indianapolis, IN 46285, USA or Lilly France, F-67640 Fegersheim, France.

Vials manufactured by Eli Lilly and Company, Indianapolis, IN 46285, USA or Hospira, Inc., Lake Forest, IL 60045, USA or Lilly France, F-67640 Fegersheim, France.

Cartridges manufactured by Lilly France, F-67640 Fegersheim, France for Eli Lilly and Company, Indianapolis, IN 46285, USA.

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