

CLINICAL CAPSULES

Infliximab for Ulcerative Colitis

Infliximab significantly reduced the rate of colectomy in patients who had severe or moderately severe ulcerative colitis that was refractory to conventional treatment, reported Gunnar Järnerot, M.D., of Örebro (Sweden) University Hospital, and associates.

In an interim analysis of a randomized, double-blind trial that was ended early because of slow enrollment and ethical issues, significantly fewer patients (7 of 24) who received an infusion of infliximab had a colectomy within 90 days than did pa-

tients who received placebo (14 of 21). Treatment with infliximab was associated with a significant, nearly fivefold higher likelihood of remaining free of colectomy than was placebo. Two additional patients in each group had a colectomy after 6 months of follow-up (Gastroenterology 2005;128:1805-11).

Maintenance treatment with repeated infliximab infusions will probably be needed for patients with ulcerative colitis, just as it has been for patients with Crohn's disease, especially "in patients who escape a colectomy to avoid further hospitalizations

and risk of later surgery," Geert D'Haens, M.D., of the Imelda GI Clinical Research Center, Bonheiden, Belgium, said in an editorial (Gastroenterology 2005;128:2161-4). Centocor, the maker of infliximab (Remicade), did not sponsor the trial.

Mycobacterial Cause of Crohn's?

Mycobacterium avium subspecies *paratuberculosis* is present in gut tissues from a significantly greater percentage of patients with Crohn's disease than from those with ulcerative colitis or diseases not specifically related to inflammatory bowel disease, according to a prospective study.

Nested polymerase chain reaction de-

tected the DNA sequence IS900, which identifies *Mycobacterium avium* subspecies *paratuberculosis* (MAP), in 52 of 100 diseased biopsy samples from patients with Crohn's disease vs. 2 of 100 samples from patients with ulcerative colitis and 5 of 100 normal tissue biopsies from patients with diseases not specifically related to inflammatory bowel disease (Gut 2005;54:944-9).

Frank Autschbach, M.D., of the University of Heidelberg (Germany) and his colleagues reported that in patients with Crohn's disease, MAP was significantly more prevalent in diseased locations of the colon than the ileum, and in patients who had the disease for less than 15 years, compared with those who had it for 15 years or more. MAP did not occur more often with either stricturing or penetrating phenotypes of the disease. The investigators' findings are in direct contrast with reports on strong associations between polymorphisms of the *NOD2* and *CARD15* genes and patients with early-onset ileal Crohn's disease with a stricturing phenotype, said R. Balfour Sartor, M.D., of the University of North Carolina, Chapel Hill, in an editorial (Gut 2005;54:896-8).

Maintaining Remission in Crohn's

Withdrawal from azathioprine is not equivalent to continued therapy with the drug in Crohn's disease patients who have been in clinical remission for at least 3.5 years while on azathioprine, according to a randomized, double-blind trial.

Marc Lémann, M.D., of the Centre Hospitalier Universitaire Lariboisière-Saint-Louis, Paris, and his associates found that 3 (8%) of 40 patients who continued to receive azathioprine relapsed after 18 months vs. 9 (21%) of 43 patients on placebo. The trial was designed to determine whether withdrawal from azathioprine had an efficacy similar to continued treatment with azathioprine. The investigators determined that baseline levels of C-reactive protein of 20 mg/L or greater and hemoglobin less than 12 g/dL, as well as 50 or more months without steroids, were independent factors associated with a higher rate of relapse during the 18-month study (Gastroenterology 2005;128:1812-8).

Sleep Apnea: Risk for Liver Injury

Severe obstructive sleep apnea appears to be a risk factor for elevated liver enzymes and steatohepatitis, independent of body weight, reported Florence Tanné of Hôpital Saint-Antoine, Paris, and colleagues.

In a prospective study of 163 patients who were evaluated for clinical suspicion of obstructive sleep apnea (OSA), the researchers found that OSA was severe in 44 patients, moderate in 84, and absent in 35 patients. Body mass index and severe OSA were independently associated with elevated liver enzymes in a multivariate analysis. Of 32 patients with elevated liver enzymes, 18 underwent liver biopsy (Hepatology 2005;41:1290-6).

In 12 of 13 patients with a liver biopsy who had steatosis, evidence of steatohepatitis (lobular necrosis or hepatocyte ballooning) was seen. Patients with severe OSA had significantly higher levels of insulin, greater insulin resistance, and higher percentages of steatosis and scores of lobular necrosis and fibrosis than did those with either moderate OSA or no OSA.

—Jeff Evans

NovoLog[®] Mix 70/30

70% insulin aspart protamine suspension and 30% insulin aspart injection, (rDNA origin)

Mealtimes and in-between times

BRIEF SUMMARY. PLEASE CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

NovoLog[®] Mix 70/30 is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

CONTRAINDICATIONS

NovoLog Mix 70/30 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog Mix 70/30 or one of its excipients.

WARNINGS

Because NovoLog Mix 70/30 has peak pharmacodynamic activity one hour after injection, it should be administered with meals.

NovoLog Mix 70/30 should not be administered intravenously. NovoLog Mix 70/30 is not to be used in insulin infusion pumps. NovoLog Mix 70/30 should not be mixed with any other insulin product.

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog Mix 70/30. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Glucose monitoring is recommended for all patients with diabetes.

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 (rDNA versus animal-source insulin) 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 NovoLog Mix 70/30 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).

Fixed ratio insulins are typically dosed on a twice daily basis, i.e. before breakfast and supper, with each dose intended to cover two meals or a meal and snack. Because there is diurnal variation in insulin resistance and endogenous insulin secretion, variability in the time and content of meals, and variability in the time and extent of exercise, fixed ratio insulin mixtures may not provide optimal glycemic control for all patients. The dose of insulin required to provide adequate glycemic control for one of the meals may result in hyper- or hypoglycemia for the other meal. The pharmacodynamic profile may also be inadequate for patients (e.g. pregnant women) who require more frequent meals.

Adjustments in insulin dose or insulin type may be needed during illness, emotional stress, and other physiologic stress in addition to changes in meals and exercise.

The pharmacokinetic and pharmacodynamic profiles of all insulins may be altered by the site used for injection and the degree of vascularization of the site. Smoking, temperature, and exercise contribute to variations in blood flow and insulin absorption. These and other factors contribute to inter- and intra-patient variability.

Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

Hypoglycemia - As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog Mix 70/30. 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 - Clinical or pharmacology studies with NovoLog Mix 70/30 in diabetic patients with various degrees of renal impairment have not been conducted. As with other insulins, the requirements for NovoLog Mix 70/30 may be reduced in patients with renal impairment.

Hepatic Impairment - Clinical or pharmacology studies with NovoLog Mix 70/30 in diabetic patients with various degrees of hepatic impairment have not been conducted. As with other insulins, the requirements for NovoLog Mix 70/30 may be reduced in patients with hepatic impairment.

Allergy - Local Reactions - Erythema, swelling, and pruritus at the injection site have been observed with NovoLog Mix 70/30 as with other insulin therapy. Reactions may be related to the insulin molecule, other components in the insulin preparation including protamine and cresol, components in skin cleansing agents, or injection techniques.

Systemic Reactions - 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 myalgias have been reported with the use of cresol as an injectable excipient.

Antibody production - Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in the 3-month, open-label comparator trial as well as in a long-term extension trial. Changes in cross-reactive antibodies were more common after NovoLog Mix 70/30 than with Novolin[®] 70/30 but these changes did not correlate with change in HbA1c or increase in insulin dose. The clinical significance of these antibodies has not been established. Antibodies did not increase further after long-term exposure (>6 months) to NovoLog Mix 70/30.

Information for patients - Patients should be informed about potential risks and advantages of NovoLog Mix 70/30 therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose

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, NovoLog at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area) had no direct adverse effects on male and female fertility, or on general reproductive performance of animals.

Pregnancy-Teratogenic Effects-

Pregnancy Category C

Animal reproduction studies have not been conducted with NovoLog Mix 70/30. However, reproductive toxicology and teratology studies have been performed with NovoLog (the rapid-acting component of NovoLog Mix 70/30) 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 10 U/kg/day (approximately three times the human subcutaneous 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 rabbits based on U/body surface area.

It is not known whether NovoLog Mix 70/30 can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or NovoLog in pregnant women. NovoLog Mix 70/30 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers - It is unknown whether NovoLog Mix 70/30 is excreted in human milk as is human insulin. There are no adequate and well-controlled studies of the use of NovoLog Mix 70/30 or NovoLog in lactating women.

Pediatric Use - Safety and effectiveness of NovoLog Mix 70/30 in children have not been established.

Geriatric Use - Clinical studies of NovoLog Mix 70/30 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

ADVERSE REACTIONS

Clinical trials comparing NovoLog Mix 70/30 with Novolin 70/30 did not demonstrate a difference in frequency of adverse events between the two treatments.

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

Body as whole: Allergic reactions (see PRECAUTIONS, Allergy).

Skin and Appendages: Local injection site reactions or rash or pruritus, as with other insulin therapies, occurred in 7% of all patients on NovoLog Mix 70/30 and 5% on Novolin 70/30. Rash led to withdrawal of therapy in <1% of patients on either drug (see PRECAUTIONS, Allergy).

Hypoglycemia: see WARNINGS and PRECAUTIONS.

Other: Small elevations in alkaline phosphatase were observed in patients treated in NovoLog controlled clinical trials. There have been no clinical consequences of these laboratory findings.

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.

More detailed information is available on request.

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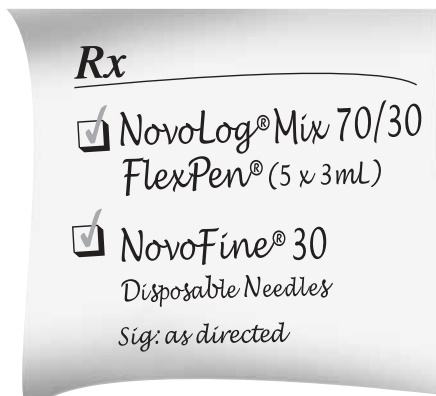
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monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction for use of injection devices, and proper storage of insulin.

Female patients should be advised to discuss with their physician if they intend to, or if they become, pregnant because information is not available on the use of NovoLog Mix 70/30 during pregnancy or lactation (see PRECAUTIONS, Pregnancy).

Laboratory Tests - The therapeutic response to NovoLog Mix 70/30 should be assessed by measurement of serum or blood glucose and glycosylated hemoglobin.

Drug Interactions A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring. 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. 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).

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 medical products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

Mixing of Insulins

NovoLog Mix 70/30 should not be mixed with any other insulin product.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog Mix 70/30. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog, the rapid-acting component of NovoLog Mix 70/30, at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog 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