

High Intake of Animal Protein Tied to IBD Risk

VITALS

Major Finding: The relative risk for developing IBD was 3.31 for high total protein intake and 3.03 for high animal protein intake, when comparing the highest tertile of intake with the lowest tertile of intake.

Data Source: A prospective study of a cohort of approximately 60,000 women aged 40-65 years, 77 of whom developed IBD during a mean follow-up of 10 years.

Disclosures: Dr. Jantchou said that he had no financial conflicts to disclose.

BY HEIDI SPLETE

FROM A TELECONFERENCE IN
ADVANCE OF THE ANNUAL
DIGESTIVE DISEASE WEEK

High intake of animal protein was significantly associated with increased risk of developing inflammatory bowel disease in a prospective study of more

than 60,000 women aged 40-65 years, 77 of whom developed IBD.

Although doctors have long suspected an association between diet and inflammatory bowel disease (IBD), most previous studies on this topic have been retrospective, said Dr. Prévost Jantchou of the Centre for Research in Epidemiology

and Population Health in Villejuif, France.

In this prospective study, onset of IBD occurred after the first dietary questionnaire was completed by each participant, so it was not necessary for the women to try to recall what they had eaten in the past—a common source of error in retrospective studies.

The 77 cases, all of whom developed confirmed IBD, were part of the E3N study, a cohort of more than 60,000 women that was established in France in 1990 to assess risk factors for female cancers. The controls were all the women in the cohort of 60,000 who did not state that they had developed IBD by 2005, the final follow-up. A Cox survival model analysis was performed.

The participants completed questionnaires about diet, disease incidence, and lifestyle every 2 years until 2005. The average follow-up period for the women in this study was 10 years.

Dr. Jantchou and colleagues examined participants' intake of protein, carbohydrate, and fat. Then the subjects were divided into three groups based on protein intake. The average intake of the low, middle, and high tertiles was 1.08 g/kg, 1.52 g/kg, and 2.07 g/kg, respectively. The Food and Drug Administration recommends an average daily protein intake of 0.8 g/kg of body weight, he said.

More than two-thirds of the 77 participants who developed IBD had an elevated protein intake, Dr. Jantchou noted. Mean total protein intake was 102.4 g/day for IBD cases vs. 92.1 g/day for controls, Dr. Jantchou said in an interview. Animal protein intake also was higher for the women who developed IBD during the study: 70.1 g/day, vs. 61.9 g/day for the controls, he said.

Overall, a high intake of animal protein was associated with a significantly increased risk of IBD. The relative risks for the highest tertile of intake vs. the lowest tertile were 3.31 for total protein intake and 3.03 for animal protein intake specifically. The associations remained significant after researchers controlled for smoking and hormone therapy, both of which can increase the risk for IBD.

When the investigators looked at specific animal proteins, they found that higher than average consumption of meat or fish was associated with a significantly increased risk of IBD but the high consumption of dairy products or eggs was not, Dr. Jantchou said.

When IBD was broken down into Crohn's disease and ulcerative colitis, similar results were seen for both diseases: High intake of animal protein was associated with an increased risk of each disease. The researchers found no association between either carbohydrate intake or fat intake and risk of IBD, he noted.

This study is the first to prospectively show an association between a high intake of animal protein and an increased risk of IBD, Dr. Jantchou said. "The next step we want to take is to look at animal protein in patients already diagnosed with IBD and to give them dietary advice," Dr. Jantchou added. ■

Table 3. Incidence and Rate of Hypoglycemia^a in Placebo-Controlled Clinical Studies when JANUVIA was used as Add-On Therapy to Glimepiride (with or without Metformin) or Insulin (with or without Metformin), Regardless of Investigator Assessment of Causality

Add-On to Glimepiride (+/- Metformin) (24 weeks)	JANUVIA 100 mg + Glimepiride (+/- Metformin)	Placebo + Glimepiride (+/- Metformin)
	N=222	N=219
Overall (%)	27 (12.2)	4 (1.8)
Rate (episodes/patient-year) ^b	0.59	0.24
Severe (%) ^c	0 (0.0)	0 (0.0)
Add-On to Insulin (+/- Metformin) (24 weeks)	JANUVIA 100 mg + Insulin (+/- Metformin)	Placebo + Insulin (+/- Metformin)
	N=322	N=319
Overall (%)	50 (15.5)	25 (7.8)
Rate (episodes/patient-year) ^b	1.06	0.51
Severe (%) ^c	2 (0.6)	1 (0.3)

^aAdverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required; intent-to-treat population.

^bBased on total number of events (i.e., a single patient may have had multiple events).

^cSevere events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the overall incidence of adverse reactions of hypoglycemia was 1.2% in patients treated with JANUVIA 100 mg and 0.9% in patients treated with placebo.

In the study of JANUVIA as add-on combination therapy with metformin and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on JANUVIA and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on JANUVIA and 1.0% in patients given add-on placebo.

In the 24-week, placebo-controlled factorial study of initial therapy with JANUVIA in combination with metformin, the incidence of hypoglycemia was 0.6% in patients given placebo, 0.6% in patients given JANUVIA alone, 0.8% in patients given metformin alone, and 1.6% in patients given JANUVIA in combination with metformin.

In the study of JANUVIA as initial therapy with pioglitazone, one patient taking JANUVIA experienced a severe episode of hypoglycemia. There were no severe hypoglycemia episodes reported in other studies except in the study involving co-administration with insulin.

Laboratory Tests. Across clinical studies, the incidence of laboratory adverse reactions was similar in patients treated with JANUVIA 100 mg compared to patients treated with placebo. A small increase in white blood cell count (WBC) was observed due to an increase in neutrophils. This increase in WBC (of approximately 200 cells/microL vs placebo, in four pooled placebo-controlled clinical studies, with a mean baseline WBC count of approximately 6600 cells/microL) is not considered to be clinically relevant. In a 12-week study of 91 patients with chronic renal insufficiency, 37 patients with moderate renal insufficiency were randomized to JANUVIA 50 mg daily, while 14 patients with the same magnitude of renal impairment were randomized to placebo. Mean (SE) increases in serum creatinine were observed in patients treated with JANUVIA [0.12 mg/dL (0.04)] and in patients treated with placebo [0.07 mg/dL (0.07)]. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

Postmarketing Experience. The following additional adverse reactions have been identified during postapproval use of JANUVIA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions include anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome [see *Warnings and Precautions*]; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis [see *Limitations of Use; Warnings and Precautions*].

USE IN SPECIFIC POPULATIONS

Pregnancy. *Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies 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. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a registry to monitor the pregnancy outcomes of women exposed to JANUVIA while pregnant. Health care providers are encouraged to report any prenatal exposure to JANUVIA by calling the Pregnancy Registry at (800) 986-8999.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30- and 20-times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Nursing Mothers. Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUVIA is administered to a nursing woman.

Pediatric Use. Safety and effectiveness of JANUVIA in pediatric patients under 18 years of age have not been established.

Geriatric Use. Of the total number of subjects (N=3884) in preapproval clinical safety and efficacy studies of JANUVIA, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter. [See *Dosage and Administration*.]

For detailed information, please read the Prescribing Information.

Rx only



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