

Celiac Disease Therapies Show Early Promise

BY ALICIA AULT

Associate Editor, Practice Trends

SAN DIEGO — Two new therapeutic approaches to celiac disease modestly improved patients' gluten tolerance, based on the results of early studies reported at a press briefing at the annual Digestive Disease Week.

The results of a third small trial indicated that the diagnostic criteria for celiac disease may be too strict, leaving many pa-

tients with early-stage disease undiagnosed and untreated.

Celiac disease is a T-cell-mediated autoimmune disorder characterized by small intestinal inflammation, injury, and intolerance to gluten found in wheat, rye, and barley products. Celiac disease affects about 6.5 million people worldwide and 3 million people in the United States. The small intestine primarily is affected, but the disorder is associated with a wide range of other systemic effects including malnutri-

tion, bone mineral loss, anemia, and delayed growth. Treatment is limited to a gluten-free diet, but dietary adherence is difficult and response to diet is poor in up to 30% of patients.

Results were presented from a phase IIIb study of larazotide acetate (AT-1001), a novel oral drug that inhibits intestinal barrier dysfunction and is being developed by Baltimore-based Alba Therapeutics Corp. Dr. Daniel Leffler and his colleagues—from the Beth Israel Deaconess Medical

Center, Boston; the Mayo Clinic, Rochester, Minn.; and the South Hills Endoscopy Center in Pittsburgh—reported on 86 patients who had biopsy-proven celiac disease and were in remission for at least 6 months. Subjects were randomized to one of seven treatment arms, including placebo and various doses of the active drug, with or without a gluten challenge, for 14 days. The drug was taken three times daily with meals.

The primary end point was intestinal permeability, as measured by the urinary lactulose/mannitol ratio. Among the 69 patients who completed the study, the primary outcome was not met in the 14-day study period. In ad hoc analyses, however, permeability was significantly improved by day 21, reported Dr. Leffler of the divisions of clinical nutrition and gastroenterology.

Alba aims to launch a larger phase II study, and planning for phase III has already begun, he said. The drug was well

Depression	2	2	2	2	2
Respiratory, Thoracic and Mediastinal Disorders					
Pharyngolaryngeal pain	2	1	3	3	2

*PGB: pregabalin

Other Adverse Reactions Observed During the Clinical Studies of LYRICA Following is a list of treatment-emergent adverse reactions reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse reactions are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the **Warnings and Precautions** section. **Body as a Whole** — *Frequent*: Abdominal pain, Allergic reaction, Fever, *Infrequent*: Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction, Suicide attempt, *Rare*: Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional Injury, Retroperitoneal Fibrosis, Shock, Suicide. **Cardiovascular System** — *Infrequent*: Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope, *Rare*: ST Depressed, Ventricular Fibrillation. **Digestive System** — *Frequent*: Gastroenteritis, Increased appetite; *Infrequent*: Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare*: Aphthous stomatitis, Esophageal Ulcer, Periodontal abscess. **Hemic and Lymphatic System** — *Frequent*: Eczyemosis; *Infrequent*: Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare*: Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocytopenia. **Metabolic and Nutritional Disorders** — *Rare*: Glucose Tolerance Decreased, Urate Crystalluria. **Musculoskeletal System** — *Frequent*: Arthralgia, Leg cramps, Myalgia, Myasthenia; *Infrequent*: Arthrosis; *Rare*: Chondrodystrophy, Generalized Spasm. **Nervous System** — *Frequent*: Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Infrequent*: Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperkinesia, Hyperkinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia, *Rare*: Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extraparaindial syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticolis, Trismus. **Respiratory System** — *Rare*: Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn. **Skin and Appendages** — *Frequent*: Pruritus, *Infrequent*: Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare*: Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Nail Disorder, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule. **Special senses** — *Frequent*: Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent*: Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare*: Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis. **Urogenital System** — *Frequent*: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence; *Infrequent*: Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, Urine abnormality; *Rare*: Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis, Ovarian disorder, Pyelonephritis. **Comparison of Gender and Race** The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race. **Post-marketing Experience** The following adverse reactions have been identified during postapproval use of LYRICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Nervous System Disorders** — Headache. **Gastrointestinal Disorders** — Nausea, Diarrhea

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C. Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) ≥ 5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at ≥ 1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established. When pregnant rabbits were given LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD. In a study in which female rats were dosed with LYRICA (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at ≥ 100 mg/kg and offspring survival was decreased at ≥ 250 mg/kg. The effect on offspring survival was pronounced at doses ≥ 1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at ≥ 250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD. There are no adequate and well-controlled studies in pregnant women. LYRICA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effects of LYRICA on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥ 50 times the mean human exposure (AUC₀₋₂₄) of 123 $\mu\text{g}\cdot\text{hr}/\text{mL}$ at the maximum recommended clinical dose of 600 mg/day. **Nursing Mothers** It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and efficacy of pregabalin in pediatric patients have not been established. In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses ≥ 50 mg/kg. The neurobehavioral changes of acoustic startle persisted

at ≥ 250 mg/kg and locomotor activity and water maze performance at ≥ 500 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established. **Geriatric Use** In controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 246 patients were 65 to 74 years of age, and 73 patients were 75 years of age or older. In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older. In controlled clinical studies of LYRICA in epilepsy, there were only 10 patients 65 to 74 years of age, and 2 patients who were 75 years of age or older. No overall differences in safety and efficacy were observed between these patients and younger patients. In controlled clinical studies of LYRICA in fibromyalgia, 106 patients were 65 years of age or older. Although the adverse reaction profile was similar between the two age groups, the following neurological adverse reactions were more frequent in patients 65 years of age or older: dizziness, vision blurred, balance disorder, tremor, confusional state, coordination abnormal, and lethargy. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment [see *Dosage and Administration*].

DRUG ABUSE AND DEPENDENCE

Controlled Substance LYRICA is a Schedule V controlled substance. LYRICA is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior). **Abuse** In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, LYRICA (450mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30mg, single dose). In controlled clinical studies in over 5500 patients, 4% of LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. **Dependence** In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache or diarrhea [see *Warnings and Precautions*], suggestive of physical dependence.

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans There is limited experience with overdose of LYRICA. The highest reported accidental overdose of LYRICA during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse reactions experienced by patients exposed to higher doses (≥ 900 mg) were not clinically different from those of patients administered recommended doses of LYRICA. **Treatment or Management of Overdose** There is no specific antidote for overdose with LYRICA. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with LYRICA. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

PATIENT COUNSELING INFORMATION

Patient Package Insert Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA. **Angioedema** Patients should be advised that LYRICA may cause angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Patients should be instructed to discontinue LYRICA and immediately seek medical care if they experience these symptoms [see *Warnings and Precautions*]. **Hypersensitivity** Patients should be advised that LYRICA has been associated with hypersensitivity reactions such as wheezing, dyspnea, rash, hives, and blisters. Patients should be instructed to discontinue LYRICA and immediately seek medical care if they experience these symptoms [see *Warnings and Precautions*]. **Dizziness and Somnolence** Patients should be counseled that LYRICA may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on LYRICA to gauge whether or not it affects their mental, visual, and/or motor performance adversely [see *Warnings and Precautions*]. **Weight Gain and Edema** Patients should be counseled that LYRICA may cause edema and weight gain. Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure [see *Warnings and Precautions*]. **Abrupt or Rapid Discontinuation** Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea [see *Warnings and Precautions*]. **Ophthalmological Effects** Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician [see *Warnings and Precautions*]. **Creatine Kinase Elevations** Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever [see *Warnings and Precautions*]. **CNS Depressants** Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence. **Alcohol** Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedating effects of alcohol. **Use in Pregnancy** Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy [see *Use in Specific Populations*]. **Male Fertility** Men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain. **Dermatopathy** Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials.



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DR. GREEN

tolerated and undetectable in serum, making it a potentially safe addition or alternative to a gluten-free diet, said Dr. Leffler.

Working with Alvine Pharmaceuticals Inc., Dr. Peter Watson, of the Belfast City (Ireland) Hospital Trust performed a double-blind crossover study of another therapeutic designed to aid gluten digestion.

For the study, 20 celiac disease patients were randomly assigned to receive 5 g of gluten pretreated with a combination of enzymes or 5 g of untreated enzymes. The enzymes, prolyl endopeptidase and endopeptidase-B2, were synthesized from microorganisms and barley. The enzymes hypothetically could help celiac disease patients fully digest gluten and thus avoid inflammation and symptoms, said Dr. Watson.

After treatment, there was no significant difference in symptom profiles, but 10 patients had a decrease in fecal fat levels, indicating increased gluten tolerance.

Dr. Peter H. Green, director of the celiac disease center at Columbia University, New York, hailed the two studies, saying that they indicated a potential for patients to have a treatment besides diet, which is notoriously difficult to follow. "It's very exciting for [researchers] and patients that the pharmaceutical industry has started to study this," he said.

Currently, the diagnosis of celiac disease is confirmed by a biopsy showing small bowel mucosal villous atrophy with crypt hyperplasia (Marsh III).

But Dr. Markku Mäki of the University of Tampere (Finland) presented results of a randomized, prospective study that indicate damage from celiac disease occurs gradually, with clinical symptoms

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'Optical Biopsy' Safe and Effective for Endoscopy

BY ROBERT FINN
San Francisco Bureau

SAN DIEGO — Two studies presented at the annual Digestive Disease Week indicate that confocal laser endoscopy increases diagnostic yield and is both accurate and safe.

The studies suggest that one day it may be possible to skip a step in the diagnosis and treatment of Barrett's esophagus, Dr. Kerry B. Dunbar said in a news confer-



'One of the great promises of confocal microscopy is that we instantly get a diagnosis.'

DR. DUNBAR

ence. Dr. Dunbar was the senior author of the randomized study and a coauthor of the retrospective study.

In confocal laser endoscopy (CLE), an endoscope is equipped with a microscope that magnifies living cells close to the surface of the GI tract 1,000 times. When used in conjunction with intravenous contrast agents such as fluorescein, acriflavine, and cresyl violet, the microscope allows endoscopists to visualize the abnormal cell growth characteristic of cancerous lesions.

In one study, investigators retrospectively combined the results of 2,102 CLE examinations on 1,771 patients at three academic medical centers. They found the "optical biopsy" technique to be 91% accurate, compared with standard biopsy. Moreover, the technique changed the ini-

Continued from previous page

appearing well before histologic damage.

Dr. Mäki and his colleagues at Tampere and the University of Helsinki identified 23 patients out of 145 consecutive cases who had only intraepithelial lymphocytosis with or without crypt hyperplasia. These 23 patients were randomized either to a gluten-free diet or a normal diet. A year later, clinical, serologic, and histologic exams were repeated. Villous architecture had deteriorated, and symptoms and antibody titers were unchanged in the normal diet group.

Symptoms, antiglutin antibodies, and mucosal inflammation were all significantly reduced in those who restricted gluten, Dr. Mäki said.

Dr. Mäki urged more studies before changing diagnostic criteria, but recommended considering celiac disease in all symptomatic patients and a trial of dietary restriction.

Dr. Green said that until a serum-based diagnostic test was available, intestinal biopsies were likely to remain the diagnostic standard.

Fewer than 5% of Americans with celiac disease have been diagnosed, Dr. Green estimated. "We're all looking for an easier way [than biopsy] to diagnose this disorder." ■

tial diagnosis in 32% of the upper GI examinations and 22% of examinations of the lower GI tract.

The other study was a prospective, controlled, crossover trial in which 36 patients underwent both CLE and standard endoscopy (in random order and separated by 2-6 weeks) to identify areas of dysplasia in Barrett's esophagus. The two techniques uncovered about the same number of sites with high-grade dysplasia, but CLE required 60% fewer mucosal biopsies to do so.

Furthermore, 9 of 15 patients (60%) at high risk of high-grade dysplasia and 14 of 21 patients (67%) undergoing surveillance endoscopy following a Barrett's diagnosis required no mucosal biopsies at all during their CLE procedures, because the investigators detected no suspicious sites.

"One of the great promises of confocal microscopy is that we instantly get a diagnosis: 'Aha, here's the area of dysplasia. I'm going to do a mucosal resection now.' And the patient only gets one sedated

procedure," said Dr. Dunbar of Johns Hopkins University, Baltimore.

Dr. Dunbar said she had no relevant conflicts of interest, but disclosed that one of the investigators in the retrospective study received unrestricted research funding from Pentax, which manufactures a CLE system. The randomized study was funded by the National Institutes of Health and by a research award from the American Society of Gastrointestinal Endoscopy. ■

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