

# An Elemental Diet Is a Last Resort in Esophagitis

BY BRUCE JANCIN  
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KEYSTONE, COLO. — Use of an elemental diet in patients with eosinophilic esophagitis is extremely effective—albeit draconian, disruptive, and seldom necessary, Dr. David M. Fleischer said at a meeting on allergy and respiratory disease sponsored by the National Jewish Medical and Research Center.

“We don’t want to eliminate all foods,

because it’s hard on the patient. They’re more likely to cheat on that diet,” according to Dr. Fleischer, a pediatric allergist at the center.

“We don’t usually put patients on an elemental diet, because we want them to be able to eat other foods. So we spend the time to find out what foods they can’t eat and take them out of the diet,” he said.

He and his colleagues rely upon skin prick testing and radioallergosorbent tests for meats, grains, eggs, and a limited number of the other major food antigens in constructing individualized elimination diets. Patch testing is utilized at some other centers.

The reliability of all of these tests is questionable; results need to be correlated with clinical findings.

“It’s more of an art than a science. It can be complicated to figure out what the offending foods are,” he conceded.

That being said, modern elemental formula liquid diets don’t taste as bad as they used to, and they are nutritionally fairly complete, needing only supplemental calcium and a few other nutrients for long-term use, Dr. Fleischer continued.

Multiple studies demonstrate that the use of an elemental diet in children with eosinophilic esophagitis is effective in 92%-98% of cases. Symptoms resolve in 7-10 days.

The esophageal eosinophilia drops from the 15 or more cells per high-power field (HPF) required for the diagnosis to zero cells or close to it in 4-5 weeks.

Elimination diets guided by allergy testing are often nearly as effective.

A low-cost, no-hassle alternative elimination diet has been described by pediatric gastroenterologist Dr. Amir Kagalwalla and coworkers at Northwestern University, Chicago. They dispensed with allergy testing and instead simply removed six of the most common aller-

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genic foods from the diets of 35 children with eosinophilic esophagitis. The excluded foods were milk, soy, wheat, egg, peanut, and seafood.

Upon repeat esophageal biopsy at least 6 weeks later, esophageal inflammation was significantly improved to 10 or fewer eosinophils/HPF in 26 of the 35 children (74%). From a mean baseline of 80 cells, the posttreatment average fell to 13.6 eosinophils/HPF. The histologic response was associated with clinical improvement (Clin. Gastroenterol. Hepatol. 2006;4:1097-102).

But the on-treatment eosinophil count achieved with this approach remained well above normal.

And that makes Dr. Fleischer uneasy. “We don’t know what it means long term. Will it prevent esophageal strictures?” he wondered.

As part of the same retrospective observational study, Dr. Kagalwalla and colleagues also assigned 25 children to a liquid elemental diet. Esophageal eosinophilia dropped from a mean baseline of 59 cells/HPF to 3.7 cells/HPF. Twenty-two of the 25 treated patients (88%) experienced a significant reduction in esophageal inflammation as defined by a reduction to not more than 10 eosinophils/HPF.

Most patients with eosinophilic esophagitis also respond to antiallergy medication.

For example, having patients swallow inhaled corticosteroids so the topical medication coats the esophagus quiets their esophageal inflammation. When the regimen is stopped, however, the eosinophilic esophagitis returns. ■

## LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia (2% and <1%). \*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). †Denominator used was for females only (N=490 Lexapro; N=404 placebo). ‡Generalized Anxiety Disorder Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 428 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder† (Lexapro (N=429) and Placebo (N=427)).

Autonomic Nervous System Disorders: Headache (24% and 17%); Paresthesia (2% and 1%); Central & Peripheral Nervous System Disorders: Headache (24% and 17%); Paresthesia (2% and 1%); Gastrointestinal Disorders: Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Rhabdomyolysis (2% and 1%); Toothache (2% and 0%). General: Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%); Musculoskeletal: Neck/Shoulder Pain (3% and 1%); Psychiatric Disorders: Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). Urinary: Ejaculation Disorder<sup>†</sup> (14% and 2%); Anorgasmia<sup>†</sup> (6% and <1%); Menstrual Disorder (2% and 1%). \*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). †Denominator used was for females only (N=247 Lexapro; N=232 placebo). Dose Dependency of Adverse Events The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. TABLE 4. Incidence of Common Adverse Events\* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=252); Insomnia (4%, 7%, 14%); Diarrhea (5%, 6%, 14%); Dry Mouth (2%, 4%, 9%); Somnolence (1%, 4%, 9%); Dizziness (2%, 4%, 7%); Sweating increased (<1%, 3%, 8%); Constipation (1%, 3%, 6%); Fatigue (2%, 2%, 6%); Indigestion (1%, 2%, 6%). \*Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. Male and Female Sexual Dysfunction with SSRIs Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 5 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. TABLE 5. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Lexapro (N=407) and Placebo (N=383)); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=737) and Placebo (N=636)); Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. Vital Sign Changes Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. Weight Changes Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. Laboratory Changes Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. ECG Changes Electrocardiograms from (N=225), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. Other Events Observed During the Premarketing Evaluation of Lexapro Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 2 & 3, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; cardiovascular - frequent: palpitation, hypertension, infrequent: bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - frequent: light-headed feeling, migraine, infrequent: tremor, vertigo, restless legs, staking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - frequent: heartburn, abdominal cramp, gastroenteritis, infrequent: gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - frequent: allergy, pain in limb, fever, hot flushes, chest pain, infrequent: edema of extremities, chills, lightheadedness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Hematologic and Lymphatic Disorders - frequent: bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - frequent: increased weight, infrequent: decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - frequent: arthralgia, myalgia, infrequent: jaw stiffness, muscle cramp, muscle stiffness, arthralgia, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - frequent: appetite increased, lethargy, irritability, concentration impaired, infrequent: jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female† - frequent: menstrual cramps, menstrual disorder, infrequent: menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. \*% based on female subjects only. N= 905 Respiratory System Disorders - frequent: bronchitis, sinus congestion, coughing, nasal congestion, sinus headache, infrequent: asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - frequent: rash, infrequent: pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodules. Special Senses - frequent: vision blurred, tinnitus, infrequent: taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - frequent: urinary frequency, urinary tract infection, infrequent: urinary urgency, kidney stone, dysuria, blood in urine. Events Reported Subsequent to the Marketing of Escitalopram - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gall, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, choreo-thetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prothrombinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

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## Questions About the Epidemiology Remain

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KEYSTONE, COLO. — Does the sharp escalation in diagnoses of eosinophilic esophagitis in the past several decades reflect a true emerging epidemic of a relatively new disease, or is it merely an artifact of greater physician recognition?

The truth most likely lies somewhere in between, Dr. David M. Fleischer asserted at a meeting on allergy and respiratory disease sponsored by the National Jewish Medical and Research Center.

Eosinophilic esophagitis was first described in 1977. Epidemiologic studies suggest the worldwide incidence in both children and adults is climbing and may now exceed that of inflammatory bowel disease.

Eosinophilic esophagitis has been characterized by some as “eczema of the esophagus.” And indeed, the increase in the disorder mirrors the well-documented rise in recent decades of the more traditional manifestations of atopy—food allergy, atopic dermatitis, allergic rhinitis, and asthma.

How common is eosinophilic esophagitis? When gastroenterologists at the Karolinska Institute, Stockholm, conducted a population-based study in which they performed esophagogastroduo-

denoscopy in 1,000 randomly selected adult volunteers, they found 1.1% had 15 or more intraepithelial eosinophils per high-power field (Gut 2007;56:615-20), thereby fulfilling the pathologic portion of the diagnostic criteria for eosinophilic esophagitis.

Pediatric gastroenterologists in Ohio estimated the prevalence of eosinophilic esophagitis in youths up to age 19 years at

4 per 10,000 in 2003 (N. Engl. J. Med. 2004;351:940-1). And a blinded retrospective evaluation of esophageal biopsies at a tertiary pediatric gastroenterology clinic in Western Australia showed a rapidly increasing prevalence of eosinophilic esophagitis, from 0.05 cases per 10,000 children in 1995 to 0.89 per 10,000 in 2004 (Arch. Dis. Child. 2006;91:1000-4).

But with the exception of the Swedish study, these reports are susceptible to ascertainment bias. Moreover, while the annual number of PubMed citations on eosinophilic esophagitis has grown exponentially since 1978, only 29% of them were original studies; the rest were case reports or review articles.

That rate of growth in turn suggests awareness of eosinophilic esophagitis on the part of gastroenterologists, allergists, and pathologists is growing at a considerably faster pace than any actual ad-

vance in scientific understanding.

The implication is that increased physician recognition of the GI disorder is contributing—to an as-yet uncertain extent—to the apparent rise in incidence and prevalence, observed Dr. Fleischer, a pediatric allergist at the center.

Although the epidemiology of eosinophilic esophagitis is incompletely understood, it is known that males account for 75%-80% of cases, consistent with the strong male predilection for food allergy. It is clearly an allergic disease. Most affected patients have a personal and family history of allergic disease. Some also display seasonal variation in their GI symptoms.

Moreover, roughly 80% of patients with eosinophilic esophagitis have elevated serum total IgE and display sensitization to food or environmental allergens on skin prick tests, patch testing to foods, and/or RAST testing, Dr. Fleischer continued.

Biopsy specimens of esophageal mucosa in affected individuals show eosinophils, T cells, and mast cells, suggestive of chronic TH-2-associated inflammation. Elevated levels of TH-2 cytokines such as interleukin-5 and interleukin-13 are also present.

Further underscoring the allergic nature of eosinophilic esophagitis is the fact that most affected patients respond to antiallergy therapy, whether it be swallowed inhaled corticosteroids or food elimination or elemental diets, Dr. Fleischer noted. ■