Gluten Causes Symptoms in Only Half of Patients in Glutox Trial

Written by Lynne Lederman, PhD

Nonceliac gluten sensitivity (NCGS) is characterized by gastrointestinal (GI) and systemic symptoms that occur soon after gluten ingestion and resolve when gluten is withdrawn [Di Sabatino A et al. *Clin Gastroenterol Hepatol*. 2015]. However, some question the existence of NCGS and the role of gluten. Other food components could be responsible, and there are no well-established, defined diagnostic criteria for NCGS.

Luca Elli, MD, PhD, Center for the Prevention and Diagnosis of Celiac Disease, Milan, Italy, presented the results of the multicenter Glutox Trial [NCT01864993], which was designed to determine if gluten is associated with symptoms in patients who respond to a gluten-free diet (GFD).

Glutox was an Italian double-blind placebo-controlled challenge (DBPCC) trial that enrolled patients (n = 100) from outpatient gastroenterologic services. Eligible patients included adults with functional GI symptoms (eg, irritable bowel syndrome, dyspepsia) based on the Rome III criteria for functional GI disorders. Patients with known celiac disease, wheat allergy, or ongoing GFD were excluded. Patients were evaluated for symptoms and global satisfaction with the SF-36 Health Survey Update and the visual analog scale (VAS).

After enrollment, patients followed a GFD for 21 days. Those who responded with a change in VAS ≥ 3 cm were randomly assigned to 7 days of gluten or placebo. Gluten was administered in 800-mg capsules, 7 capsules per day (5.6 g per day); placebo was an equivalent amount of rice starch. After a 7-day washout period, patients crossed over to the other treatment. Patients followed a GFD during the entire study. At study end, NCGS was defined as a change in VAS ≥ 3 cm for gluten vs placebo.

During the GFD before randomization, responders (n = 81) were identified as those with improvement in abdominal pain, stool consistency, bloating, postprandial fullness, early satiety, epigastric pain, or other symptoms and in the physical and mental component summaries of global satisfaction.

During the DBPCC portion of the trial, patients who received gluten experienced a significant reduction in global VAS score ($P = .05$). Patients who reacted positively to gluten during this portion of the trial had worsening of their abdominal pain, stool consistency satisfaction, and bloating, with a decrease in both the physical and mental component summary scores. These patients were considered to have potential NCGS (n = 25). No demographic or biochemical marker was identified that was associated with a positive response to the gluten challenge. There was no effect of capsule sequence. About half (13 of 25) of patients reacting to gluten in the DBPCC portion of the trial received gluten first and placebo second.

Table 1. Demographics Before and After GFD and Double-Blind Placebo-Controlled Challenge

	At Enrollment	GFD Responders	Potential NCGS
Patients, n	100	81	25
Female, %	90	88	96
Age, median, y	38 ± 11	38 ± 10	37 ± 11
BMI, median, kg/m^2	21 ± 4	20 ± 4	21 ± 4
Dyspepsia, n	36	25	10
IBS, n	55	48	13
Other GI conditions, n	9	8	2

BMI, body mass index; GFD, gluten-free diet; GI, gastrointestinal; IBS, irritable bowel syndrome; NCGS, nonceliac gluten sensitivity.

The demographics of patients at enrollment, those who responded to the GFD, and those who had potential NCGS were similar (Table 1).

The Glutox Trial is ongoing. Further investigation may answer some questions raised by this trial. It is not known if DBPCC can be used to select GFD responders or diagnostically investigate functional GI symptoms. Fifty-six percent of enrolled patients who responded to the GFD did not react to the gluten DBPCC, suggesting that they may be sensitive to other dietary components, which remain to be identified.

Eluxadoline Shows Efficacy for IBS-D in IBS3001 and IBS3002 Phase 3 Trials

Written by Lynne Lederman, PhD

Irritable bowel syndrome with diarrhea (IBS-D), a common gastrointestinal (GI) disorder, is characterized by bloating, urgency, recurring abdominal pain, and loose, frequent stools in the absence of structural or biochemical abnormalities. Endogenous μ- and d-opioid receptors are critical for the normal function and sensation of the GI tract. A novel mixed μ-opioid receptor agonist and d-opioid receptor antagonist, eluxadoline, acts locally in the GI tract with low systemic absorption and oral bioavailability [Fujita W et al. *Biochem Pharmacol*. 2014].

William D. Chey, MD, University of Michigan Health System, Ann Arbor, Michigan, USA, discussed the results of IBS3001 [NCT01553591] and IBS3002 [NCT01553747], 2 randomized, double-blind, placebo-controlled, phase 3

trials that evaluated the sustained efficacy of twice-daily treatment with eluxadoline in adults with IBS-D.

Both studies randomly assigned adults 1:1:1 to placebo twice daily, eluxadoline 75 mg BID, or eluxadoline 100 mg BID. Both studies were 26 weeks, and efficacy was assessed at week 12 for the FDA and at week 26 for the European Medicines Agency. IBS3002, conducted in the United States, United Kingdom, Canada, and Puerto Rico, concluded at 26 weeks. For IBS3001, conducted in the United States, United Kingdom, and Canada, treatment was extended for an additional 26 weeks to assess the safety of long-term use.

Inclusion criteria comprised IBS-D (Rome III criteria), average worst abdominal pain (WAP) score >3 (scale 0 to 10), average stool consistency Bristol Stool Scale (BSS) score ≥5.5 (scale 1 to 7), at least 5 days with a BSS score ≥5.5 during the 4-week screening period, and IBS-D global symptom score ≥2.0 (scale 0 to 4). Patients with inflammatory bowel or celiac disease, prior pancreatitis, sphincter of Oddi dysfunction, and other GI conditions or elevated lipase, alanine, or aspartate aminotransferases were excluded.

The composite efficacy end point was response, evaluated at weeks 1 through 12 (FDA primary end point) and weeks 1 through 26 (European Medicines Agency primary end point). Responders were defined as having an improvement in daily pain (WAP scores improved by ≥30% in the past 24 hours compared with average baseline pain) and daily stool consistency (BSS score <5) on at least 50% of days.

Baseline characteristics of enrolled patients in IBS3001 (n=1282) and IBS3002 (n=1146) were comparable. Mean BSS and WAP were both >6, indicating a severely affected population. Efficacy results are shown in Figure 1.

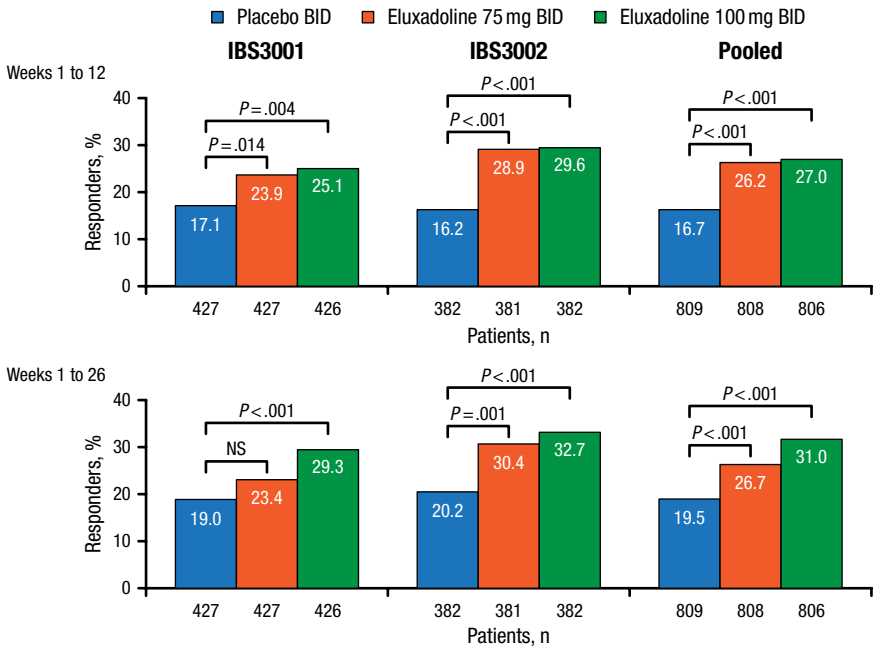
Efficacy of eluxadoline was seen within week 1, with maximum benefit achieved in weeks 4 to 6 and sustained over the 6-month efficacy evaluation period. Efficacy was seen in both men and women. Significantly more patients taking either eluxadoline dose reported ≥75% urgency-free days ($P<.001$) and decrease in bowel movement frequency ($P<.001$) than those taking placebo.

Adverse events were reported slightly more often by those in the eluxadoline groups; GI-related events were the most common.

Sphincter of Oddi spasm events occurred in 10 patients taking eluxadoline who had prior cholecystectomy; symptoms were reversible with withdrawal of drug. Pancreatitis occurred in 4 patients in the eluxadoline groups. No deaths or surgery resulted from these events.

To conclude, eluxadoline offers an effective new therapeutic option for patients with IBS-D; however, a risk of mild pancreatitis was seen.

Figure 1. Primary Composite Efficacy End Point



NS, not significant.

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