GERD

Novel approach to treatment

Up to 30% of patients with GERD remain symptomatic despite being on standard PPI regimens. Inhibition of metabotropic glutamate receptors (mGluRs) reduces transient lower esophageal sphincter (LES) relaxation episodes and increases LES tone in animals, and now a potent, selective modulator of mGluR5, ADX10059, has been shown to reduce acid reflux in patients with GERD.

Keywood and colleagues conducted a randomized, single-blind, placebo-controlled trial in 24 patients with GERD. The patients received oral placebo before each of three high-fat meals on the first day, and either oral ADX10059 50 mg or 250 mg before each of three high-fat meals on the second day. 24 h esophageal pH measurements showed that ADX10059 250 mg three times daily significantly decreased the percentage of time at pH <4 from 7.2% to 3.6%. This dose also reduced esophageal acid exposure throughout the 24 h period and significantly reduced the number and duration of symptomatic reflux episodes. The 50 mg dose of ADX10059 was not significantly superior to placebo.

ADX10059 was generally well tolerated. Commonly reported adverse events in the high-dose group (dizziness and nausea) are consistent with the mechanism of action and rapid absorption of the drug. A modified-release formulation of ADX10059 has been developed to reduce its central nervous system side effects, and this will be used in subsequent studies.

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Original article Keywood, C. *et al.* A proof-of-concept study evaluating the effect of ADX10059, a metabotropic glutamate receptor-5 negative allosteric modulator, on acid exposure and symptoms in gastro-esophageal reflux disease. *Gut* **58**, 1192–1199 (2009).