

Naloxegol for Opioid-Induced Constipation in Patients with Noncancer Pain

William D. Chey, M.D., Lynn Webster, M.D., Mark Sostek, M.D., Jaakko Lappalainen, M.D., Ph.D., Peter N. Barker, Ph.D., and Jan Tack, M.D., Ph.D.

This article was published on June 4, 2014, at NEJM.org.

Presented by: Ali Khaleifa R3 Palliative Care June 17 2014
Palliative Care Unit Grey, Nuns Hospital ,Edmonton,Alberta

ABSTRACT

Background

Opioid-induced constipation is common and debilitating. We investigated the efficacy and safety of naloxegol, an oral, peripherally acting, μ -opioid receptor antagonist, or the treatment of opioid-induced constipation.

Methods

In two identical phase 3, double-blind studies (study 04, 652 participants; study 05, 700 participants), outpatients with noncancer pain and opioid-induced constipation were randomly assigned to receive a daily dose of 12.5 or 25 mg of naloxegol or placebo.

The primary end point was the 12-week response rate (≥ 3 spontaneous bowel movements per week and an increase from baseline of ≥ 1 spontaneous bowel movements for ≥ 9 of 12 weeks and for ≥ 3 of the final 4 weeks) in the intention-to-treat population. The key secondary end points were the response rate in the subpopulation of patients with an inadequate response to laxatives before enrollment, time to first postdose spontaneous bowel movement, and mean number of days per week with one or more spontaneous bowel movements.

Results

Response rates were significantly higher with 25 mg of naloxegol than with placebo (intention-to-treat population: study 04, 44.4% vs. 29.4%, $P = 0.001$; study 05, 39.7% vs. 29.3%, $P = 0.02$; patients with an inadequate response to laxatives: study 04, 48.7% vs. 28.8%, $P = 0.002$; study 05, 46.8% vs. 31.4%, $P = 0.01$); in study 04, response rates were also higher in the group treated with 12.5 mg of naloxegol (intention-to-treat population, 40.8% vs. 29.4%, $P = 0.02$; patients with an inadequate response to laxatives, 42.6% vs. 28.8%, $P = 0.03$). A shorter time to the first postdose spontaneous bowel movement and a higher mean number of days per week with one or more spontaneous bowel movements were observed with 25 mg of naloxegol versus placebo in both studies ($P < 0.001$) and with 12.5 mg of naloxegol in study 04 ($P < 0.001$). Pain scores and daily opioid dose were similar among the three groups. Adverse events (primarily gastrointestinal) occurred most frequently in the groups treated with 25 mg of naloxegol.

Conclusions

Treatment with naloxegol, as compared with placebo, resulted in a significantly higher rate of treatment response, without reducing opioid-mediated analgesia. (Funded by AstraZeneca; KODIAC-04 and KODIAC-05 ClinicalTrials.gov numbers, NCT01309841 and NCT01323790, respectively.)

Strengths:

Good study design (multicentre, adequate recruitment)
Balanced patient characteristics across study groups
Clear inclusion and exclusion criteria end point definition
Addressed and analyzed side effects.

Weaknesses:

This study was conducted in an outpatient setting, with relatively stringent exclusion criteria, which reduces its applicability
The definition of constipation and inadequate response to laxatives did not include imaging .
Supported directly by Pharmaceutical Company which could raise the commercial bias.

Relevance to palliative care:

Opioid induced constipation is very common complaint in palliative care setting. Although this could be managed with use of laxative, still proportion of patient would require opioid antagonist as last resource to reverse opiate effects on the intestinal motility. Availability of oral opioid antagonist that does not cross the blood brain barrier could provide an alternative to methylenaltroxone . If approved for cancer patient management, safety profile as well as costs associated should be considered before prescribing it in the primary palliative care setting.