Randomised controlled trial

Naloxegol increases frequency of bowel movements and combats inadequate response to laxatives

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Context

The therapeutic action of opioid analgesics is compromised by peripheral adverse effects, among which constipation is the most disabling, as laxatives often fail to provide satisfactory relief.[1] To address this problem, opioid receptor antagonists with limited systemic bioavailability (retarded naloxone) or a peripherally restricted site of action (alvimopan, methylnaltrexone) have been developed. Their use in managing opioid-induced constipation (OIC), however, is limited by narrow indication and subcutaneous administration (methylnaltrexone), approval only for short-term use because of safety concerns (alvimopan) or a fixed combination of retarded naloxone with oxycodone.[2] Naloxegol is a peripherally acting μ-opioid receptor antagonist under development as an oral, daily administered drug for the treatment of OIC.[3] Chemically, it is a pegylated derivative of naloxone, the PEG moiety making the compound a substrate for P-glycoprotein transporters which limit drug entry into the central nervous system (CNS).[3]

Methods

The paper describes two identical randomised, double-blind, placebo-controlled phase 3 trials involving a total of 1352 outpatients suffering from non-cancer pain, experiencing pain relief by stable oral opioid medication and reporting OIC, defined by less than three spontaneous bowel movements (SPMs) per week accompanied by other symptoms. Participants were assigned to receive placebo or a daily dose of 12.5 or 25 mg naloxegol for 12 weeks, and stratified such that at least 50% of the participants in each treatment arm had an inadequate response to laxatives. Achievement of three or more SPMs per week was the primary end point. Secondary end points included three or more SPMs per week among patients who previously did not respond to laxatives.

Findings

Naloxegol significantly enhanced response rates for the primary and secondary end points in a dose-dependent manner relative to placebo. In one trial, a significant increase in the response rate was seen with both doses of naloxegol, while in the other trial only the 25 mg dose had a statistically significant effect. The number needed to treat at 25 mg was 6.7 in study 1 and 9.7 in study 2. A similar dose-related effect of naloxegol was noted for secondary end points, especially response rate in patients who had responded inadequately to laxatives before enrolment. The incidence of adverse events, notably diarrhoea and abdominal pain, was highest in the 25 mg dose group.

Commentary

The results of the two phase 3 trials confirm and extend a phase 2 study of patients with OIC in whom a 4-week treatment with daily doses of 5, 25 and 50 mg naloxegol increased the number of weekly SPMs in a dose-dependent fashion.[3] In addition, the current data indicate that patients who have an inadequate response to laxatives benefit from the use of naloxegol. The absence of withdrawal symptoms and pain exacerbation indicate that the drug ameliorates OIC by a peripheral site of action but does not interfere with the analgesic effect of opioid analgesics within the CNS. Naloxegol is thus set to join the class of peripherally active opioid receptor antagonists that do not enter the CNS. Naloxegol may claim significant advantages over other members of the class in terms of indication, route of administration, flexibility of use and safety; however, it has not yet been proven to be equally efficacious in attenuating OIC. This issue is difficult to judge since no comparative trial results are yet available, while clinical trials involving individual drugs are difficult to compare because they differ in their clinical end points or in the way they were analysed.

Apart from opioid-receptor-related adverse events (diarrhoea, abdominal pain) which can be interpreted as manifestations of gastrointestinal opioid withdrawal, naloxegol appears to be fairly safe over a 12-week treatment period.[2] At the dose of 25 mg/day, naloxegol lacks a clinically relevant effect on cardiac repolarisation in healthy volunteers.[4] Although naloxegol is primarily cleared by a hepatic route, mild or moderate hepatic impairment has minimal effects on the pharmacokinetics and safety of the drug, while renal impairment may necessitate dose adjustments.[5 6]

Competing interests None.

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