Peer Review File

Article information: https://dx.doi.org/10.21037/apm-22-1130

Reviewer A

I think this is worthwhile to publish. Quality is low because retrospective study of few patients, but still relevant for the population being studied. Main criticism is under point 3, inconsistent and unclear reporting of the key data.
Concerns:
1) authors should explain in introduction what the drug is, and how it differs from other commonly used drugs in this class, such as naloxegol and methylnaltrexone.
Reply: Thank you for your insightful comments. We have added the following sentences (see page 4, lines 25-28, page 5, lines 1-2): "The other PAMORAs, methylnaltrexone and naloxegol, used in the United States and Europe were designed to act peripherally selectively by modifying naltrexone and naloxone. Methylnaltrexone contains a quaternary ammonium salt and naloxegol has a polyethylene glycol chain, and these unique substructures allow them to act in a peripherally selective manner. Naldemedin, on the other hand, is a new drug that combines high oral absorption and low cerebral translocation by introducing a carboxylic acid as a polar group into an existing naltolindole derivative, making it difficult for the drug to cross the blood-brain barrier"
2) authors should, especially for the population being studied, point out that this is NOT to be used for mechanical obstruction of GI tract, as perforations have been noted when this class of drugs used in that setting. GI cancer patients would be at high risk of same.
Reply: Thank you for your insightful comment. The risks pointed have to be taken into account when using this class of drugs in patients with gastrointestinal tumors, which was the population analyzed in this study. We have added the following sentences (see page 9, lines 13-16):

"It is important to note that when administering naldemedine, adverse events include diarrhea and abdominal pain, with severe diarrhea being reported as the most serious. Prior to administration of naldemedine, it must be confirmed that the patient has no gastrointestinal obstruction or history of gastrointestinal perforation to prevent such events."
3) Question about Figure 2: 12 patients had 5 or more bowl movements in the week prior to starting the study drug. Why would they receive a drug for opioid induced constipation if they are not constipated? This should be better described in the body of the article. I presume they were being prescribed the medication prophylactically, which is not a usual use of this class of medications (PAMORAs)
Reply: Thank you for your insightful comment. We have added the following sentences (see page 9, lines 3-10): "In addition, as shown in Figure 2a, naldemedine was administered in

combination with opioids to patients who had maintained bowel movements during the week prior to naldemedine administration. Although the current analysis was retrospective and initiation of naldemedine treatment is recommended after the diagnosis of OIC, it is thought that actual cases of gastrointestinal tumors and prophylactic use of naldemedine exist in clinical practice. In this sense, the patients enrolled in the current study are cases with gastrointestinal tumors, and preventing constipation in advance may be an option to prevent serious events such as gastrointestinal perforation."

4) 2/3 of way down page 1 table 1 it states:
"Discontinuation within 7 days"
I presume they mean discontinuation of the medication within 7 days i.e. the study period.
Six of 27 patients did not complete the 7 day study period post starting the study drug. The reasons why should be discussed in the body of the text. This represents 18% of the study sample. Therefore, statistical calculations should explain how these missing data were handled
Were these 6 patients who did not complete 7 days of treatment part of the non-responder group?
Also, the 12 or so patients who were already having 5 or more BM per week, were they considered responders? Because arguably they were not constipated by definition.
Clarification around these important points are the major concern of the study.
Reply: Thank you for raising this important point. Since cases of discontinuation within one week after administration are also important in the safety analysis, we counted adverse events and defecation frequency for more than one week after discontinuation. The defecation frequency was also counted in the group of patients who dropped out during the course of treatment, and was evaluated as a whole. We have added the following sentence (see page 5, lines 21-24). "Patients who discontinue treatment within a week of naldemedine administration are also important in safety analysis, and even if discontinuation occurred within a week, adverse events and defecation frequency in the week after naldemedine initiation were counted and evaluated as a whole."

5) this statement ¾ of the way down page 1 of table one does not make sense to me:
"With or without laxatives after starting naldemedine administration" and then Yes/No response. This may be due to translation to English. I think they mean "were other laxatives continued after starting naldemedine" (yes/no). Please clarify.
Reply: We apologize for the imprecise wording. In Table 1, we have changed the text to "With or without other laxatives continued after starting naldemedine administration" as suggested.
6) two questions lower in table 1:
"Irregular use of antiemetic agents after starting naldemedine" (yes/no response). I presume the question is was there use of antiemetic agents after starting naldemedine? Answer could be regular/PRN/none?
Reply: Thank you for your comment; we have added "Irregular use of antiemetic agents after starting naldemedine administration" in Table 1, and the target patients are indicated as "Yes" or "No or unknown".

Reviewer B

Your paper is excellent, but I have a few concerns. I recommend additional analysis.

Major

1、During the first week of nardimedine treatment, how many times did you increase, discontinue, or decrease the dose of other medications for regular constipation?
How often did you increase, stop, or decrease the dose of your other regular laxatives?

Reply: Thank you for your important and insightful suggestions. We collected information on concomitant laxatives before and after the start of naldemedine treatment, but we did not collect information on changes such as dose increases, discontinuations, or dose reductions during the course of the study. We will refer to this information in our future analyses.

2、Also, did the number of rescue medications used change before and after NAL administration?

Reply: Thank you for pointing this out. As pointed out in our previous reply, we did not collect data on the number of rescue medications used before and after naldemedine administration.

3、Did you change the use of regular antiemetic medications and rescue medications?

Reply: Thank you for pointing this out. Similar to our reply above, we did not collect data on changes in the use of regular antiemetic and rescue medications.

4、Differences in background factors between responder and non-responder should be compared.

Reply: Thank you for your important suggestion. We have added the results of a multivariate logistic regression analysis of the clinical factors indicative of response in patients receiving naldemedine as Table 4, following your suggestion. We have added the following sentences (see page 8, lines 12-16): "Finally, multivariate logistic regression analysis was performed to assess the relationship between naldemedine efficacy and various clinical factors, as shown in Table 4. There were no statistically significant differences in the efficacy of naldemedine with respect to age, PS, or daily opioid dose in oral morphine equivalents."

Minor

1、 Residual bowel movements should be better described as sensation of incomplete evacuation.

Reply: Thank you for your suggestion. "Residual bowel movements" was changed to "sensation of incomplete evacuation" (see page 4, lines 16-17).

2、 Abdominal distention should be better described as abdominal bloating.

Reply: Thank you for your suggestion. "Abdominal distention" was changed to "abdominal bloating" (see page 4, line 17).

3、 Reference 13 is for AGA GL, so Japanese guideline should be additionally cited.

Reply: Thank you for your suggestion. We added the Japanese guideline (see page 4 , lines 21-22). "). The Japanese guidelines recommend peripheral μ-opioid receptor antagonists (PAMORA) for refractory OIC without opioid switching, conventional colorect-stimulating, or osmotic laxative improvement"

Reviewer C

This study was a retrospective analysis with very limited numbers of participants. Since all participants were in-hospital patients, both efficacy and safety of naldemedine were carefully monitored and well recorded by healthcare professionals.

The most critical review points are:

1) The analyzed data were part of the data in their previously published data [Ref. 16]. The authors should summarized their previous results, compare the present findings to their previous findings, and discuss the difference(s) between present and previous ones in the Introduction and/or Discussion sections.

   Reply: Thank you for your important suggestion. We have added the following sentences (see page 11, lines 1-9): "A multicenter retrospective study previously published by us evaluated the efficacy and safety of naldemedine for opioid-induced constipation in 149 patients with various cancer types (18). With regard to efficacy, the share of responders was 65.7%, with a significant increase in defecation frequency one week before and after naldemedine administration. On the other hand, with regard to safety, diarrhea was the most common adverse event (48.4%), but most events were grade 1. The results suggest that the efficacy and safety of naldemedine in clinical practice are comparable to those determined in prospective studies. In this subanalysis focusing on efficacy and safety in gastrointestinal cancers, these parameters were comparable to those in the overall population, and there were no new signals of reduced efficacy or toxicities specific to gastrointestinal tumors."

2) Efficacy and safety of naldemedine should be separately analyzed and compared in patients with upper or lower digestive tract cancers.

Reply: Thank you for your insightful comment. We have added a note on changes in defecation frequency (Figure 2b and c) and adverse events (Table 3) in upper and lower gastrointestinal tracts, respectively.

We have also added the following sentences (see page 7, lines 14-28, page 8, lines 1-2, page 8, lines 9-13): "Moreover, the number of bowel movements in the upper (esophagus and stomach) and lower gastrointestinal tracts (small and colorectal) were also analyzed separately. The median number of bowel movements during the seven days before and after naldemedine administration was three (range: 0-13) and 5.5 (range: 2-13) in the upper gastrointestinal tract, respectively, showing a trend toward increased defecation frequency after naldemedine administration (Wilcoxon signed rank test, $p = 0.0647$, Figure 2b). The median number of bowel movements during the seven days before and after naldemedine treatment was four (range: 0–10)

and seven (range: 1–39), respectively, in the lower gastrointestinal tract, with a significant increase in defecation frequency after naldemedine administration (Wilcoxon signed rank test, $p = 0.0056$, Figure 2c)." and "Moreover, adverse events in the upper (esophagus and stomach) and lower gastrointestinal tracts (small and colorectal; Table 3b, c) and at lower (< 30 mg/day of morphine equivalent) and higher opioid dosages (≥ 30 mg/day of morphine equivalent) were also demonstrated separately (Table 3d, e)."

We further added the following sentences: "In addition, changes in defecation frequency were evaluated for upper and lower gastrointestinal tumors and opioid dosages (<30/≥ 30 mg/day of morphine equivalent). Defecation frequency was statistically increased in patients with lower gastrointestinal tumors and higher opioid dosages, while there was a trend toward increased frequency in patients with upper gastrointestinal tumors. Notably, these analyses were exploratory and based on a small number of patients." and "In addition, adverse events were evaluated for upper and lower gastrointestinal tumors and opioid dosages (<30/≥ 30 mg/day of morphine equivalent). Mild diarrhea was the most common adverse event in each patient group; however, specific adverse events for each population could not be identified due to the low number of cases."

3) Efficacy and safety of naldemedine should be separately analyzed and compared in patients receiving higher or lower opioid dosages.

Reply: Thank you for your insightful comment. The median opioid use was divided into higher and lower groups with a cutoff of 30 mg/day, and changes in defecation frequency (Figures 2d and e) and adverse events (Table 3) have been added for each group.

We have also added the following sentences (see page 9, lines 15-20): "Moreover, the number of bowel movements at lower (< 30 mg/day of morphine equivalent) and higher opioid dosages (≥ 30 mg/day of morphine equivalent) were also analyzed separately. The median number of bowel movements during the seven days before and after naldemedine administration was four (range: 0-11) and six (range: 1-21) at lower opioid dosages, respectively, without a significant increase in defecation frequency after naldemedine administration (Wilcoxon signed rank test, $p = 0.17$, Figure 2d). The median number of bowel movements during the seven days before and after naldemedine treatment was three (range: 0–13) and seven (range: 2–39), respectively, at higher opioid dosages, with a significant increase in defecation frequency after naldemedine administration (Wilcoxon signed rank test, $p = 0.0033$, Figure 2e)." and "Moreover, adverse events in the upper (esophagus and stomach) and lower gastrointestinal tracts (small and colorectal; Table 3b, c) and at lower (< 30 mg/day of morphine equivalent) and higher opioid dosages (≥ 30 mg/day of morphine equivalent) were also demonstrated separately (Table 3d, e)."

We further added the following sentences: "In addition, changes in defecation frequency were evaluated for upper and lower gastrointestinal tumors and opioid dosages (<30/≥ 30 mg/day of morphine equivalent). Defecation frequency was statistically increased in patients with lower gastrointestinal tumors and higher opioid dosages, while there was a trend toward increased frequency in patients with upper gastrointestinal tumors. Notably, these analyses were

exploratory and based on a small number of patients." and "In addition, adverse events were evaluated for upper and lower gastrointestinal tumors and opioid dosages (<30/≥ 30 mg/day of morphine equivalent). Mild diarrhea was the most common adverse event in each patient group; however, specific adverse events for each population could not be identified due to the low number of cases."

Minor review points are:

1) Abstract-Results) "thrice" might be miss typing.

Reply: Thank you for your suggestion. "thrice " was changed to "three times" (see page 3, line 15).

2) The participant institutions were 10, and the retrospective study periods were more than two years. However, the study subjects were only 37 patients. The reviewer has an impression the numbers of the participants were quite small. The authors should consider why the patients receiving naldemedine were very much small in the Japanese situations.

Reply: Thank you for your insightful comment. As shown in Supplement Figure A, the analysis was limited to cases that could be observed for one week before and after treatment, which resulted in a small number of cases for the time period covered. This is described in the study limitations.

Reviewer D

I think this study is important to disclose the safety of naldemedine for the patients during cancer therapy. It is very important to identify whether brain metastasis exists or not. Because we must avoid opioid withdrawal syndrome (OWS). Please describe whether there were the patients with brain metastasis or not. Another, one patient had the adverse event of anorexia. Please describe whether this event is the symptom of OWS.

Reply: Thank you for your insightful comments. Table 1 indicates the presence or absence of central nervous system metastases, as shown in red. As pointed out, opioid withdrawal syndrome (OWS) is an important adverse event. When we checked cases of brain metastases, no cases of OWS were suspected. However, we included a small number of cases and there was a bias. We are currently analyzing the data of about 200 cases, including other cancer types, focusing on OWS, and will report our findings in the future. Thank you for your important remarks.