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Methylnaltrexone for the Relief of Constipation Due to Chronic Opioid Therapy in Advanced Illness Patients With and Without Active Cancer

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INTRODUCTION

- Opioid-induced constipation (OIC) occurs in 81% of patients taking daily oral opioids.[1] In addition, patients with and without active cancer can experience similar constipation severity[2]
- Treatment with laxatives and stool softeners is often inadequate because these approaches do not address the underlying cause of OIC, which results mainly from binding of opioids to peripheral μ-opioid receptors in the gastrointestinal (GI) tract[3-5]
- Because patients may discontinue opioid therapy or skip doses in an attempt to manage their constipation, OIC can compromise pain management[6-8]
- Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, Bridgewater, NJ, USA) is a selective, peripherally acting μ-opioid receptor antagonist that improves GI motility and transit time without affecting μ-opioid receptor–mediated analgesia[9-13]
  - MNTX is available in 2 different formulations
    - MNTX tablets and subcutaneous (SC) injection are approved for the treatment of OIC in adults with chronic noncancer pain including patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation
    - MNTX SC injection is approved for the treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care[9]
- This post hoc analysis evaluated the baseline characteristics and efficacy end points of MNTX for the treatment of OIC in advanced illness patients with and without active cancer

OBJECTIVE

- To analyze pooled data by baseline characteristics and evaluate efficacy end points from 2 studies (studies 301 and 302) in which patients with advanced illness were stratified by those with active cancer and those without

METHODS

Key Inclusion Criteria

- Aged ≥18 years with advanced medical illness (eg, illness such as incurable cancer or other end-stage illness) with a life expectancy of ≥1 month
- Receiving a scheduled, around-the-clock opioid regimen that has been stable for at least 3 days before study drug administration
- No clinically significant laxation within 48 hours before the first dose of study drug
- On stable laxative regimen for ≥3 days before the first dose of study drug
- In study 302, OIC is defined as one of the following:
  - Less than 3 bowel movements in the previous week and no clinically significant bowel movements in the previous 24 hours before the first dose of study drug
  - No clinically significant laxation within 48 hours before the first dose of study drug

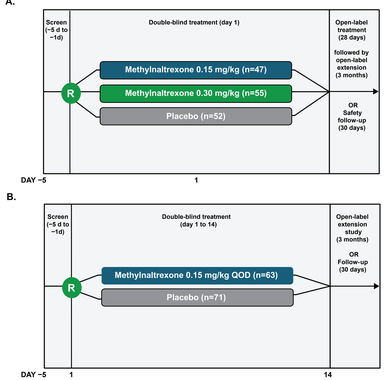
Key Exclusion Criteria

- Any disease process suggestive of gastrointestinal obstruction
- Any potential nonopioid cause of bowel dysfunction, based on the investigator's opinion
- History of or current peritoneal catheter for intraperitoneal chemotherapy or dialysis, clinically significant active diverticular disease, evidence of fecal impaction by physical examination or x-ray, surgically acute abdomen, or fecal ostomy

Study Design

- This post hoc analysis included two phase 3, multicenter, double-blind, randomized, placebo-controlled studies conducted in patients with advanced medical illness and OIC (study 301, NCT00401362; study 302, NCT00402038)
- In study 301, following IRB approval and after a 5-day screening period, patients were randomized 1:1:1 to receive single SC injections of MNTX 0.15 mg/kg, MNTX 0.30 mg/kg (above the FDA approved dose of 0.15 mg/kg), or placebo (Figure 1A)
- In study 302, following IRB approval and a 5-day screening period, patients were randomized to receive SC injections of MNTX 0.15 mg/kg or placebo every other day for 2 weeks (Figure 1B; dose escalation to 0.30 mg/kg was possible starting on day 9 at the discretion of the investigator)
- Patients who completed the studies were eligible to enroll in 28-day (study 301) or 3-month (study 302) open-label extension studies

Figure 1. Study Design for (A) Study 301 and (B) Study 302



QOD = every other day; R = randomization.

Assessments

- In this post hoc analysis, patients were stratified by those *with cancer* and those *without cancer* and analyzed by baseline characteristics and the following efficacy end points:
  - The proportion of patients with laxation response within 4 hours after the first dose of study drug
  - Time to rescue-free laxation assessed at 4 hours and 24 hours
  - Constipation distress scale, pain scores, and opioid withdrawal, assessed at 4 hours (in study 301) or on day 1 (in study 302)
    - Constipation distress was assessed using a 5-point scale (1, none; 2, little bit; 3, somewhat; 4, quite a bit; 5, very much)
    - Pain intensity was assessed using a scale from 0 (no pain) to 10 (worst possible pain)
    - Opioid withdrawal was evaluated using a modified Himmelsbach Withdrawal Scale, in which patients rated opioid withdrawal symptoms (rhinorrhea, tremor, piloerection, yawning, perspiration, restlessness, and lacrimation) on a 4-point scale (1, none; 2, mild; 3, moderate; 4, severe)
  - Global Clinical Impression of Change (GCIC) ratings (patient and clinician), assessed at 24 hours
    - The patient and investigator or staff member rated the overall change in bowel status since baseline based on the following 7-point Global Clinical Impression of Change scale (1, much worse; 2, somewhat worse; 3, slightly worse; 4, no change; 5, somewhat better; 6, slightly better; 7, much better)

Statistical Analyses

- Data from both studies were pooled and patients were stratified by those *with active cancer* and those *without active cancer*
- Efficacy analyses were performed on the intent-to-treat (ITT) analysis set, which was defined as all randomized patients who received at least 1 double-blind dose of study drug; the safety analysis set was the same as the ITT analysis set
- Comparisons between the MNTX and placebo groups were analyzed using chi-square test for the percentage of patients with laxation response; pairwise log-rank test for time to first laxation; Fisher's exact test for the percentage of patients with improvement from baseline in constipation distress scores; paired t-test for mean change from baseline in constipation distress scores; and t-test for mean change from baseline in pain scores
- The nominal level of significance was 0.05, with no adjustment for multiplicity

RESULTS

Patients

- After pooling the study populations, there were 123 placebo patients (84 *with cancer*) and 164 MNTX patients (119 *with cancer*), including 109 in the MNTX 0.15 mg/kg group (74 *with cancer*)
- Baseline characteristics stratified by presence of cancer are presented in Table 1
  - Although baseline opioid use was higher in patients *with cancer* versus patients *without cancer*, constipation distress was similar in the 2 groups
  - Despite taking an average of greater than 2 laxatives at baseline, patients in all groups had a high level of constipation distress
  - Baseline current and worst pain scores were also similar among all study groups

Table 1. Baseline Characteristics Stratified by the Presence of Cancer in Patients (Pooled ITT Population[a])

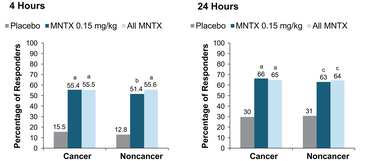
	Cancer Patients			Noncancer Patients		
Characteristic	Placebo (n=84)	MNTX 0.15 mg/kg (n=74)	All MNTX (n=119)	Placebo (n=39)	MNTX 0.15 mg/kg (n=35)	All MNTX (n=45)
Baseline MED, mg						
Median (range)	192.5 (15.0–10160)	196.5 (20.0–122560)	195.0 (12.0–122560)	72.0 (8.0–560.0)	90.0 (9.0–2170.0)	90.0 (9.0–2170.0)
Mean (SD)	620.2 (1635.1)	2319.8 (14247)	1983.9 (11630)	104.0 (106.4)	255.1 (419.9)	258.4 (433.2)
P value vs noncancer	0.0516	0.3944	0.3221	—	—	—
Number of laxatives concurrently being used, mean (SD)	2.5 (1.4)	2.2 (1.2)	2.1 (1.2)	2.4 (1.1)	2.5 (1.6)	2.8 (1.8)
Constipation distress of quite a bit or very much, no. of patients (%)	48 (57.1)	45 (60.8)	73 (61.3)	23 (59.0)	20 (57.1)	24 (53.3)
Current pain score, mean (SD)	3.1 (2.4)	3.2 (2.6)	3.2 (2.6)	3.7 (3.1)	4.0 (3.0)[b]	3.7 (2.9)[c]
Worst pain score, mean (SD)	5.5 (2.6)	5.6 (2.8)	5.4 (2.8)	4.9 (3.0)	5.8 (2.7)[d]	5.6 (2.8)[e]

MED = morphine equivalent dose; MNTX = methylnaltrexone; SD = standard deviation; ITT = intent to treat; SD = standard deviation.
[a]The ITT population includes all randomized patients who received ≥1 dose of study drug; [b]n=33; [c]n=43; [d]n=32; [e]n=42.

Laxation Response

- Similar percentages of patients *with cancer* and *without cancer* experienced laxation within 4 hours after the first dose of study drug (Figure 2)
  - In both populations, significantly greater percentages of patients experienced a laxation response within 4 hours after the first dose of MNTX compared with placebo

Figure 2. Percentage of Responders With Laxation Within 4 Hours and 24 Hours After the First Dose of Study Drug (Pooled ITT Population)

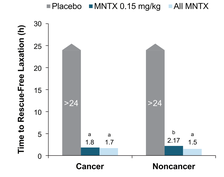


ITT = intent to treat; MNTX = methylnaltrexone.
Among patients with cancer, n=84 for placebo; n=74 for MNTX 0.15 mg/kg; and n=119 for all MNTX. Among patients without cancer, n=39 for placebo; n=35 for MNTX 0.15 mg/kg; and n=45 for all MNTX.
[a]P<0.0001; [b]P<0.001; [c]P<0.01 vs placebo.

Time to Rescue-Free Laxation

- MNTX significantly (*P*≤0.001) and rapidly improved time to rescue-free laxation versus placebo for both patients *with cancer* and *without cancer* up to 4 (not shown) and 24 hours (Figure 3) after dosing
- The median time to rescue-free laxation was 1.8 hours for the MNTX 0.15 mg/kg group and 1.7 hours for the all MNTX group in patients *with cancer* compared with a median time of >24 hours for the placebo group
- The median time to rescue-free laxation was 2.17 for the MNTX 0.15 mg/kg group and 1.5 hours for the all MNTX group in patients *without cancer* compared with a median time of >24 hours for the placebo group

Figure 3. Median Time to Rescue-Free Laxation Evaluated at 24 Hours (Pooled ITT Population)

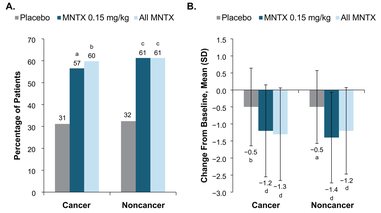


ITT = intent to treat; MNTX = methylnaltrexone.
Among patients with cancer, n=84 for placebo; n=74 for MNTX 0.15 mg/kg; and n=119 for all MNTX. Among patients without cancer, n=39 for placebo; n=35 for MNTX 0.15 mg/kg; and n=45 for all MNTX.
[a]P<0.0001; [b]P≤0.001 vs placebo.

Constipation Distress

- Improvements from baseline in constipation distress were similar in patients *with cancer* and *without cancer* (Figure 4)
  - Significantly greater improvements in constipation distress were observed in patients treated with MNTX compared with patients receiving placebo in both groups

Figure 4. (A) Percentage of Patients With Improvement From Baseline and (B) Mean Change From Baseline in Constipation Distress Score at 4 Hours (Study 301) or on Day 1 (Study 302; Pooled ITT Population)

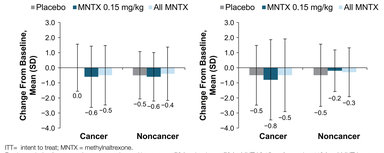


ITT = intent to treat; MNTX = methylnaltrexone; SD = standard deviation.
For the percentage of patients with improvement in constipation distress: among patients with cancer, n=84 for placebo; n=74 for MNTX 0.15 mg/kg; and n=119 for all MNTX; among patients without cancer, n=39 for placebo; n=35 for MNTX 0.15 mg/kg; and n=45 for all MNTX. For the mean change from baseline in constipation distress: among patients with cancer, n=77 for placebo; n=69 for MNTX 0.15 mg/kg; and n=111 for all MNTX; among patients without cancer, n=37 for placebo; n=31 for MNTX 0.15 mg/kg; and n=41 for all MNTX.
[a]P<0.01; [b]P<0.001; [c]P≤0.05; [d]P<0.0001 vs placebo for percentage of patients with improvement and vs baseline for mean change from baseline.

Pain Intensity

- No significant changes from baseline in current and worst pain scores were observed in patients *with cancer or without cancer* who were treated with MNTX compared with those receiving placebo (Figure 5)

Figure 5. Mean (SD) Change From Baseline in Current and Worst Pain Score at 4 Hours (Study 301) or on Day 1 (Study 302; Pooled ITT Population)

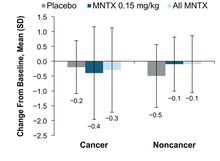


ITT= intent to treat; MNTX = methylnaltrexone.
For the analysis of current pain: among patients with cancer, n=76 for placebo; n=70 for MNTX 0.15 mg/kg; and n=113 for all MNTX; among patients without cancer, n=38 for placebo; n=31 for MNTX 0.15 mg/kg; and n=41 for all MNTX. For the analysis of worst pain: among patients with cancer, n=76 for placebo; n=68 for MNTX 0.15 mg/kg; and n=111 for all MNTX; among patients without cancer, n=38 for placebo; n=30 for MNTX 0.15 mg/kg; and n=40 for all MNTX.

Opioid Withdrawal

- Opioid withdrawal symptoms were not evident in patients *with cancer or without cancer* (Figure 6)
  - Mean changes from baseline in opioid withdrawal total scores were not significant in MNTX-treated versus placebo-treated patients

Figure 6. Mean (SD) Change From Baseline in Opioid Withdrawal Total Score at 4 Hours (Study 301) or on Day 1 (Study 302; Pooled ITT Population)

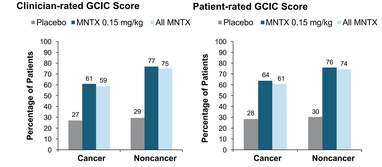


ITT = intent to treat; MNTX = methylnaltrexone; SD = standard deviation.
Among patients with cancer, n=75 for placebo; n=71 for MNTX 0.15 mg/kg; and n=114 for all MNTX. Among patients without cancer, n=38 for placebo; n=32 for MNTX 0.15 mg/kg; and n=42 for all MNTX.

Clinician- and Patient-Rated GCIC in OIC

- Patients *with cancer* and *without cancer* who were treated with MNTX experienced greater clinician- and patient-rated global improvements in OIC compared with placebo-treated patients (Figure 7)

Figure 7. Percentage of Patients With Improvement From Baseline in Clinician- and Patient-rated GCIC Score (Pooled ITT Population)[a]



GCIC = Global Clinical Impression of Change; ITT = intent to treat; MNTX = methylnaltrexone.
Percentages based on number of subjects with nonmissing measures: among patients with cancer, n=74 for placebo; n=69 for MNTX 0.15 mg/kg; and n=111 for all MNTX; among patients without cancer, n=34 for placebo; n=26 for MNTX 0.15 mg/kg; and n=36 for all MNTX.
[a]Patient and Clinician GCIC ratings were recorded at 24 hours and 7 days after administration of study drug in the 301 and 302 studies, respectively.

CONCLUSIONS

- MNTX effectively promoted laxation within 4 hours of dosing and reduced time to rescue-free laxation in advanced-illness patients *with* and *without active cancer*
- Although cancer patients were on higher opioid doses at baseline, they had similar improvements in signs and symptoms of OIC after MNTX treatment
- SC administration of MNTX allowed patients to continue their opioid treatment while experiencing a reduction in constipation distress with no signs or symptoms of opioid withdrawal and no increases in pain scores

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DISCLOSURES

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