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Efficacy and Tolerability of Subcutaneous Methylnaltrexone in Advanced Illness Patients With Opioid-Induced Constipation: a Responder Analysis

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INTRODUCTION

- Opioid-induced constipation (OIC) is a distressing adverse effect of chronic opioid therapy, evidenced in up to 90% of patients taking long-term opioids[1]
  - OIC may cause alterations in opioid use patterns (eg, reduction in dose), leading to inadequate pain control[2]
- OIC is largely mediated by μ-opioid receptors in the gastrointestinal tract[3]
- Methylnaltrexone (Relistor®, Salix Pharmaceuticals, Inc., Raleigh, NC, USA) is a selective, peripherally acting μ-opioid receptor antagonist that has restricted ability to cross the blood–brain barrier; it is indicated for the treatment of OIC in patients with advanced illness who are receiving palliative care and have had an insufficient response to laxatives[1]
  - Methylnaltrexone efficacy and safety in patients with advanced illness and OIC has been demonstrated in 2 randomized, placebo-controlled, phase 3 studies (301 and 302)[4,5]; however, demographic and baseline characteristics that may influence optimal responsiveness to methylnaltrexone have not been elucidated

OBJECTIVE

- Examine the potential influence of demographic and baseline characteristics on efficacy and tolerability of subcutaneous methylnaltrexone in patients with advanced illness and OIC

METHODS

Study Design

- 2 randomized, double-blind, placebo-controlled, phase 3, multicenter studies (301 and 302) were pooled for analysis[4,5]
  - Study 301 was a single-dose study of subcutaneous methylnaltrexone (0.15 or 0.30 mg/kg) versus placebo
  - Study 302 was a 14-day, multiple-dose study of subcutaneous methylnaltrexone 0.15 mg/kg versus placebo administered every other day

Study Population[4,5]

- Patients were ≥18 years of age with advanced illness
- Eligible patients in Study 301 had a life expectancy of 1-6 months and OIC (no clinically significant bowel movement in 48 hours), were receiving a stable opioid and laxative regimen, and were enrolled in a hospice or palliative care program
- Eligible patients in Study 302 had a life expectancy of ≥1 month and OIC (<3 bowel movements in the last week, or no bowel movement in 24-48 hours), were receiving stable doses of laxatives and opioids, and were enrolled in a hospice, nursing home, or palliative care program

Efficacy

- A primary efficacy measure in both studies was the percentage of patients with a rescue-free bowel movement within 4 hours after a single dose or first dose[4,5]
- Results were analyzed by the following demographic and baseline characteristic subgroups: sex (female vs male), age (<65 vs ≥65 years), primary diagnosis (cancer vs noncancer), baseline constipation-related distress score (≤3 vs >3; 1 = none, 2 = a little bit, 3 = somewhat, 4 = quite a bit, and 5 = very much), and baseline morphine equivalent dose (<150 vs ≥150 mg/d)
- Chi-square test was employed to evaluate results based on subgroup analyses

Safety

- Safety was assessed at 24 hours for Study 301 and daily during the 14 days of Study 302[4,5]; adverse events were pooled for the methylnaltrexone groups (0.15 and 0.30 mg/kg) and the placebo groups and were assessed across subgroups

RESULTS

Patient Disposition and Demographics

- Demographics and baseline characteristics were generally similar among treatment groups (Table 1)[4,5]

Table 1. Patient Demographics and Baseline Characteristics[4,5]

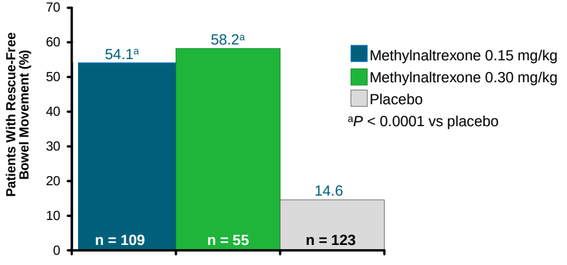
Characteristic, n (%)		Methylnaltrexone 0.15 mg/kg (n = 110)[a]	Methylnaltrexone 0.30 mg/kg (n = 55)	Placebo (n = 123)
Age group	<65 y	42 (38.2)	24 (43.6)	61 (49.6)
	≥65 y	68 (61.8)	31 (56.4)	62 (50.4)
Sex	Male	52 (47.2)	31 (56.4)	59 (48.0)
	Female	58 (52.7)	24 (43.6)	64 (52.0)
Race	White	99 (90.0)	46 (83.6)	108 (87.8)
	Black	6 (5.4)	4 (7.3)	8 (6.5)
	Other	5 (4.5)	5 (9.1)	7 (5.7)
Primary diagnosis	Cancer	74 (67.3)	45 (81.8)	84 (68.3)
	Noncancer	36 (32.7)	10 (18.1)	39 (31.7)
Any laxative use	Yes	107 (97.3)	51 (92.7)	120 (97.6)
	No	3 (2.7)	4 (7.3)	3 (2.4)
Constipation-related distress	None	11 (10.0)	4 (7.3)	14 (11.4)
	A little bit	13 (11.8)	7 (12.7)	16 (13.0)
	Somewhat	18 (16.4)	12 (21.8)	21 (17.1)
	Quite a bit	33 (30.0)	19 (34.5)	36 (29.3)
	Very much	33 (30.0)	13 (23.6)	35 (28.5)
	Not reported	2 (1.8)	0	1 (0.8)
Oral morphine equivalent	<150 mg/d	48 (43.6)	25 (45.4)	69 (56.1)
	≥150 mg/d	62 (56.4)	30 (54.5)	54 (43.9)

[a]One patient in Study 302 in the methylnaltrexone 0.15 mg/kg group received methylnaltrexone in an unblinded manner and was included in the safety analysis but not included in the efficacy analysis.[5]

Primary Outcome – Pooled Data

- A significantly greater percentage of patients treated with subcutaneous methylnaltrexone 0.15 or 0.30 mg/kg experienced a rescue-free bowel movement within 4 hours after the first dose versus patients receiving placebo (Figure 1)

Figure 1. Rescue-Free Bowel Movement Within 4 Hours of the First Dose of Methylnaltrexone or Placebo

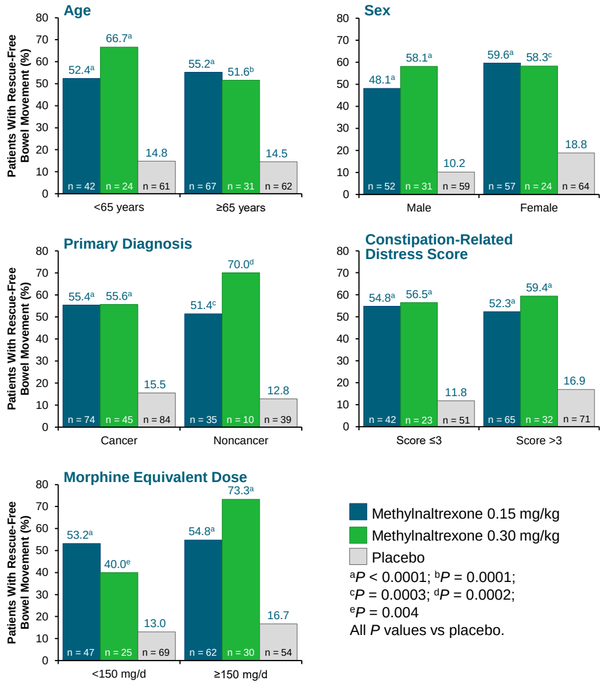


RESULTS

Subgroup Analyses

- Response to methylnaltrexone (ie, patients experiencing a rescue-free bowel movement within 4 hours after dosing) was significantly greater versus placebo for all subgroups analyzed and ranged from 40.0% to 73.3% for methylnaltrexone responses and from 10.2% to 18.8% for placebo ($P < 0.01$ for all comparisons; Figure 2)

Figure 2. Rescue-Free Bowel Movement Within 4 Hours of the First Dose of Methylnaltrexone or Placebo, by Demographic and Baseline Characteristics



RESULTS

- The largest differences in response were observed for noncancer patients (70.0% for methylnaltrexone 0.30 mg/kg vs 12.8% for placebo; $P = 0.0002$) and patients maintained on oral morphine equivalent doses ≥150 mg/d (73.3% for methylnaltrexone 0.30 mg/kg vs 16.7% for placebo; $P < 0.0001$) (Figure 2)

Adverse Events

- Overall, the most common adverse events were abdominal pain (pooled methylnaltrexone 27.9% and placebo 9.8%), flatulence (13.3% and 5.7%, respectively), and nausea (10.9% and 4.9%, respectively)
- Tolerability was generally comparable across subgroups
  - Although abdominal pain, the most commonly reported adverse event, was reported more often in patients treated with methylnaltrexone, the percentage was consistent across all subgroups (Table 2)
  - Similarly, the incidence of flatulence and nausea was consistent across subgroups

Table 2. Incidence of Abdominal Pain by Demographic and Baseline Characteristics

Results by Subgroup, patients, n/N (%)		Pooled Methylnaltrexone	Placebo
Age	<65 years	21/66 (31.8)	8/61 (13.1)
	≥65 years	25/99 (25.3)	4/62 (6.5)
Sex	Male	23/83 (27.7)	7/59 (11.9)
	Female	23/82 (28.0)	5/64 (7.8)
Primary diagnosis	Cancer	37/119 (31.1)	7/84 (8.3)
	Noncancer	9/46 (19.6)	5/39 (12.8)
Constipation-related distress score	≤3	21/65 (32.3)	3/51 (5.9)
	>3	25/98 (25.5)	9/71 (12.7)
Morphine equivalent dose	<150 mg/d	15/72 (20.8)	6/69 (8.7)
	≥150 mg/d	31/93 (33.3)	6/54 (11.1)

CONCLUSIONS

- **Across various demographic and baseline characteristic subgroups, subcutaneous methylnaltrexone produced rapid (within 4 hours) rescue-free bowel movement and was generally well tolerated**
- **Results support that the methylnaltrexone treatment effect was robust and generalizable across patient subpopulations**
  - **Particularly favorable responses in select subgroups warrants further study**

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