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Effect of Subcutaneous Methylnaltrexone on Patient-Reported Outcomes in Advanced Illness Patients With Opioid-Induced Constipation

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INTRODUCTION

- Opioid-induced constipation (OIC) is a common adverse effect of opioid therapy, with an estimated prevalence of up to 90% in patients taking long-term opioids[1]
  - Patients experience infrequent bowel movements (eg, <3 times per week) and other symptoms (eg, straining, sense of incomplete evacuation, abdominal discomfort, hard stools)[2]
- OIC can be more distressing to patients than the underlying pain syndrome and can negatively impact quality of life[3]; for example, OIC can cause patients to decrease or discontinue opioid use, leading to inadequate pain control[4]
- OIC occurs as a result of opioids binding to μ-opioid receptors in the gastrointestinal tract, which reduces motility and intestinal fluid absorption[5]
- Methylnaltrexone is a selective, peripherally acting μ-opioid receptor antagonist that has limited ability to cross the blood–brain barrier[6]; it is currently indicated for the treatment of OIC in patients with advanced illness who are receiving palliative care when response to laxative therapy has not been sufficient
  - Randomized, placebo-controlled, phase 3 studies have demonstrated the efficacy and safety of subcutaneous methylnaltrexone in inducing bowel movements in patients with advanced illness and OIC[7,8]; evaluating patient-reported outcomes has relevance for patient quality of life and treatment satisfaction, and may corroborate more objective indices of OIC

OBJECTIVE

- To assess the impact of methylnaltrexone on patient-reported outcomes in patients with advanced illness and OIC

METHODS

Study Population

- Patients ≥18 years of age with advanced illness (life expectancy ≥1 month) and OIC (<3 bowel movements in the last week or no clinically meaningful bowel movement in the last 24-48 hours) who were receiving stable doses of laxatives and opioids and were enrolled in hospice, nursing home, or palliative care programs

Study Design

- This was a randomized, double-blind, placebo-controlled, multicenter, phase 3 study[8]
  - Patients were randomly assigned to receive subcutaneous methylnaltrexone (Relistor®, Salix Pharmaceuticals, Inc., Raleigh, NC, USA) 0.15 mg/kg or placebo every other day for 2 weeks
  - If patients had <3 rescue medication–free (rescue-free) bowel movements by day 8, the initial drug volume could be doubled (from 0.15 mg/kg to 0.30 mg/kg of methylnaltrexone or equivalent volume of placebo)

Patient-Reported Outcome Evaluations

- Difficulty of each bowel movement (1 = no difficulty; 2 = slight; 3 = moderate; 4 = considerable; and 5 = great) and consistency of each bowel movement (reported as: watery, soft-formed, firm, slightly hard, hard, or very hard) were assessed daily
- Constipation-related distress (reported as: none, a little bit, somewhat, quite a bit, or very much) was assessed on days 1, 7, and 14
- Patient Global Clinical Impression of Change (GCIC) scale rating (rated as: much better, somewhat better, slightly better, no change, slightly worse, somewhat worse, and much worse) was evaluated on days 7 and 14

RESULTS

Patient Disposition and Demographics

- Demographics were generally similar between the methylnaltrexone and placebo groups: median age was 72 years (range, 34-93 y) and 70 years (range, 39-98 y); 57% and 56% of patients were female; and 97% and 92% of patients were white, respectively
- Baseline characteristics were also similar between groups (Table 1)

Table 1. Baseline Characteristics

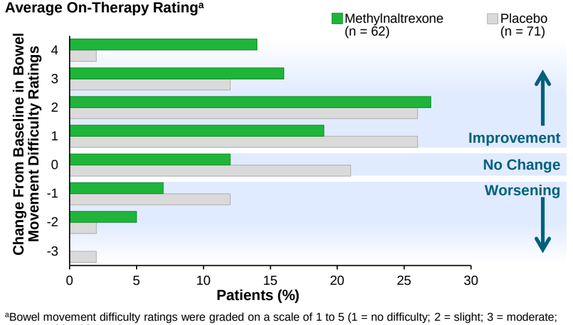
Characteristic		Methylnaltrexone 0.15 mg/kg[a] (n = 63)	Placebo (n = 71)
Primary diagnosis, n (%)	Cancer	37 (59)	41 (58)
	Noncancer	26 (41)	30 (42)
Laxative use	Any laxative use, n (%)	62 (98)	70 (99)
	No. drug classes taken, median (range)	2 (1-4)	2 (1-5)
Constipation-related distress, n (%)	None	7 (11)	8 (11)
	A little bit	6 (10)	6 (8)
	Somewhat	9 (14)	11 (15)
	Quite a bit	16 (25)	18 (25)
	Very much	22 (35)	27 (38)
	Not reported	3 (5)	1 (1)
Oral morphine equivalent, mg/d, median (range)		150 (9-4160)	100 (10-10160)

[a]One patient received methylnaltrexone in an unblinded manner and was included only in the safety analysis.

Bowel Movement Difficulty and Consistency

- Bowel movement difficulty improved more for patients receiving methylnaltrexone versus placebo, based on patient distribution analyzed by change in bowel movement difficulty between baseline and average on-therapy rating (Figure 1)
  - 77% of methylnaltrexone-treated patients reported improvement in bowel movement difficulty by ≥1 rating category versus 66% of placebo-treated patients
  - 14% of patients receiving methylnaltrexone reported improvement in bowel movement difficulty of 4 rating categories versus 2% of those receiving placebo

Figure 1. Change in Bowel Movement Difficulty Between Baseline Rating and Average On-Therapy Rating[a]

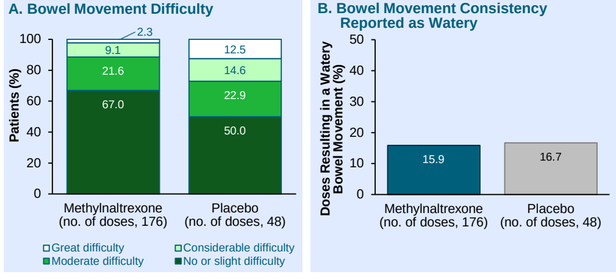


[a]Bowel movement difficulty ratings were graded on a scale of 1 to 5 (1 = no difficulty; 2 = slight; 3 = moderate; 4 = considerable; and 5 = great).

RESULTS

- For doses of methylnaltrexone and placebo that resulted in a rescue-free bowel movement within 4 hours, bowel movement difficulty was rated as "no" or "slight" difficulty for 67.0% (118 of 176) of doses in the methylnaltrexone group versus 50.0% (24 of 48) of doses in the placebo group (Figure 2A)
- Bowel movement consistency reported as watery occurred almost similarly in both groups (Figure 2B)

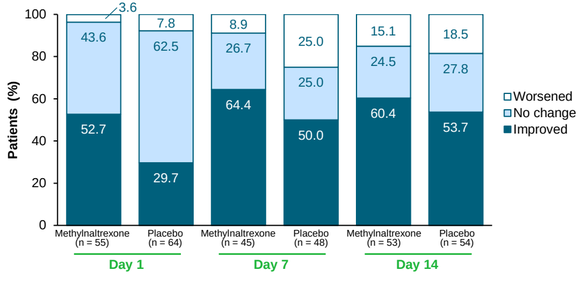
Figure 2. Bowel Movement Difficulty and Consistency for Doses That Resulted in a Rescue-Free Bowel Movement Within 4 Hours



Constipation Distress

- At baseline, 60.0% and 63.3% of patients in the methylnaltrexone and placebo groups, respectively, reported "quite a bit" or "very much" constipation-related distress
  - On day 1 of treatment, 52.7% of patients treated with methylnaltrexone reported that constipation distress had "improved" versus 29.7% of patients treated with placebo; this finding persisted for the duration of the study (Figure 3)

Figure 3. Changes From Baseline in Constipation Distress

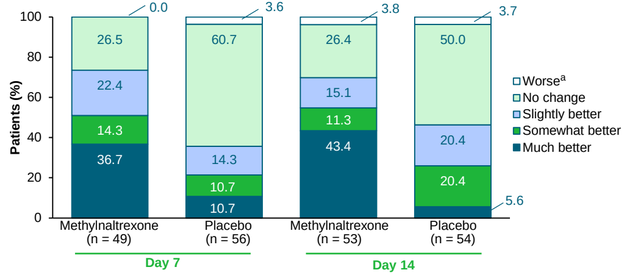


RESULTS

Patient Global Clinical Impression of Change

- Patient GCIC ratings on days 7 and 14 showed that the majority (73.5% and 67.9%, respectively) of patients in the methylnaltrexone group reported that their bowel status had improved; fewer patients in the placebo group reported that their status had improved on days 7 and 14 (35.1% and 44.6%, respectively; Figure 4)
  - More patients in the methylnaltrexone group than patients in the placebo group considered their bowel status as "much better" than at baseline on day 7 (36.7% vs 10.7%) and day 14 (43.4% and 5.6%)

Figure 4. Patient Global Clinical Impression of Change Ratings



[a]Includes responses of "much worse," "somewhat worse," and "slightly worse."

CONCLUSIONS

- **Patient-reported outcomes in this study complement previously published objective assessments of methylnaltrexone-related improvements in bowel function[8]**
- **Data support that methylnaltrexone decreases OIC symptom severity across several dimensions in patients with advanced illness**

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