Role of Alvimopan (Entereg) in Gastrointestinal Recovery And Hospital Length of Stay After Bowel Resection

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ABSTRACT

Purpose: Postoperative ileus (POI) can delay gastrointestinal (GI) recovery after bowel resection. Alvimopan (Entereg), a peripherally acting mu-opioid receptor antagonist, is thought to favorably reduce various outcome measures such as the length of stay (LOS) and time from surgery to hospital discharge following partial-bowel, large-bowel, or small-bowel resection surgery with primary anastomosis. We undertook a study to compare these outcome measures in alvimopan-treated patients undergoing laparoscopic or open-bowel resection against a control group. We also sought to determine whether any other factors—Diagnosis-Related Group (DRG) status, complications, inflammatory bowel disease, type of surgery, age, sex, intestinal cancer, diverticular disease, number of chronic conditions, and operative time—were predictive of a more favorable (shorter) time to GI recovery.

Methods: Patients' charts were retrospectively reviewed at a large 591-bed teaching hospital in suburban New York City between June and August 2010. We applied descriptive statistics for five outcome variables to compare alvimopan-treated patients with non-users. The main outcome variable was the time from surgery to hospital discharge. Secondary outcome variables were the time to pass gas, time to a liquid diet, time to a solid diet, and total LOS. We compared the outcome variables for three groups of DRG codes (329, the most complicated cases; 330, intermediate; and 331, least complicated) to determine which variables influenced these outcome measures. Multivariate analysis with stepwise multiple linear regression analysis was performed to determine independent predictors of shorter times of outcome variables.

Results: Of 80 patients, 43 received alvimopan (53.75%), and 37 (46.25%) did not. The female-to-male ratio was about 50:50 (56.25% vs. 43.75%). The mean age (standard deviation) was 66.0 (14.9) years (range, 30–92 years). In the multivariate analysis (adjusted for demographics, DRG status, type of surgery, complications, comorbidities, and operative time), for all of our outcome variables (except for time to a liquid diet), patients receiving alvimopan had shorter times to GI recovery (about 25% less) than controls did ($P < 0.05$). DRG status, complications, inflammatory bowel disease, type of surgery, and age were also significantly predictive of one or more outcome variables, whereas sex, intestinal cancer, diverticular disease, the number of chronic conditions, and operative time were not predictive of any outcomes.

Conclusion: GI recovery times were generally shorter for alvimopan-treated patients than for those who did not receive the study drug ($P < 0.05$). Alvimopan improved quality of life and reduced the cost of surgical care. This medication was considered to be a good choice for the perioperative management of patients requiring segmental bowel resection with primary anastomosis.

INTRODUCTION

Postoperative ileus (POI) is defined as an impairment of gastrointestinal (GI) motility after abdominal or other surgery. POI is characterized by abdominal distention, lack of bowel sounds, the accumulation of gas or fluid in the bowel, and delayed passage of flatus and defecation. The time to return of GI function and the ability to tolerate an oral diet are of key importance in determining hospital LOS. Patients are not discharged until they can maintain adequate oral nutrition independently.[1]

POI is associated with a longer LOS and increased utilization of health care resources. The duration of POI can vary from a few hours to several weeks. On average, the LOS of patients with POI is 5 days longer than those without POI.[1] In a study conducted in 2007, the annual national hospital cost of managing POI was $1.46 billion for both the index hospitalization and any readmissions within 30 days.[2] Various strategies, such as early removal of a nasogastric tube, early ambulation, early oral intake, the use of laxatives, a less invasive surgical procedure (such as laparoscopy), and epidural anesthesia, have been adopted in order to reduce the duration of POI.[3]

Opioids are the mainstay of postoperative control of surgical pain. Although these drugs provide excellent pain relief, their effects on the GI tract can prolong the duration of POI. Opioid medications exert both their analgesic and GI effects centrally via the mu-opioid receptor, which is located in the intestine.[3]

Alvimopan (Entereg, Adolor) is a peripherally acting mu-opioid receptor antagonist that accelerates the time to upper and lower GI recovery following partial large-bowel or small-bowel resection with primary anastomosis. Alvimopan blocks the effects of opioids in the GI tract without affecting opioid analgesia in the brain. Its inability to inhibit opioid receptors in the brain

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is a result of its limited penetration of the blood–brain barrier. In clinical trials, alvimopan significantly accelerated the time to recovery of GI function. Compared with patients receiving placebo, patients receiving alvimopan were discharged 13 to 21 hours sooner.[4]

For our study, the main goal was an overall decrease in LOS (i.e., the time from surgery to hospital discharge). Other objectives included determining the time it took for the patient to pass gas, start a liquid diet, and return to a solid diet. These outcomes are associated with improvements in the level of care provided as well as with a reduction in health care costs.

METHODS

A system analyst from the Data Retrieval and Analysis Center at Winthrop University Hospital in Mineola, N.Y., identified 84 patients who had been discharged with DRG codes 329 to 331 between June and August 2010. DRG 329 is defined as major small-bowel and large-bowel procedures with major comorbidities, DRG 330 is defined as major small-bowel and large-bowel procedures with comorbidities (not major comorbidities), and DRG 331 is defined as major small-bowel and large-bowel procedures without any comorbidities. Hence, the DRG codes used in our study can be classified as 329 (the most complicated cases), 330 (intermediate), and 331 (the least complicated).

The study included adults with DRG codes 329, 330, and 331 who underwent elective bowel resection with primary anastomosis. Patients were excluded if they had used opioids for more than 7 days immediately before surgery. Four patients were eliminated, leaving a total of 80 evaluable patients. The primary postsurgical analgesic was morphine, administered by intravenous (IV) push.

No enhanced recovery protocol was available. We based our use of alvimopan on the inclusion criteria and on the clinician's discretion. Secondary outcomes (time to pass gas, time to a liquid diet, time to a solid diet, first bowel movement, and total LOS) are always routinely documented in patient charts at our hospital. In this study, no patients in either group had a diagnosis of primary or secondary POI.

Statistical Methods

We conducted a retrospective chart review of patients who underwent laparoscopic or open-bowel resection with primary anastomosis between June and August 2010 at Winthrop University Hospital. We sought to compare the outcomes (LOS–surgery to discharge, time to pass gas, time to a liquid diet, time to a solid diet, time to a first bowel movement, and total LOS) of patients who received alvimopan with outcomes in patients who did not receive the drug. We also wanted to determine whether any other factor (e.g., DRG code, age, sex, or operative time) was an independent predictor of shorter recovery times.

Winthrop University Hospital is registered in the Entereg Access Support and Education (E.A.S.E.) program. All hospitals that dispense alvimopan must be enrolled in this program. Continuous variables are expressed as mean ± standard deviation (SD) or as medians. We compared groups (e.g., their drug status) for categorical variables (e.g., their DRG code) using Fisher's exact test or the *chi*-square test for trends.

We compared two groups for continuous variables, such as LOS, with the rank-sum test (the non-parametric analogue of the unpaired *t*-test). We used the rank-sum test because our outcome measures tend to be non-normally distributed. Our main outcome variable was time from surgery to discharge LOS. Secondary outcome variables were time to pass gas, time to a liquid diet, time to a solid diet, time to a first bowel movement, and total LOS.

We used the Kruskal–Wallis test to compare variables for three groups (e.g., DRG codes). If the overall result was statistically significant ($P < 0.05$), the Tukey's pairwise multiple comparison test ($P < 0.05$) was used to determine the source

Table 1 Descriptive Statistics of Clinical Characteristics by Drug Status

Variable	Without Alvimopan (n = 37)	With Alvimopan (n = 43)	*P* Value*
DRG [n (%)]†			0.0022
329	12 (32.4)	7 (16.3)	
330	19 (51.3)	13 (30.2)	
331	6 (16.2)	23 (53.5)	
Sex [n (%)]			0.11
Female	17 (45.9)	28 (65.1)	
Male	20 (54.1)	15 (34.9)	
Surgery type [n (%)]‡			< 0.0001
Laparoscopic	7 (19.4)	28 (65.1)	
Open	29 (80.6)	15 (34.9)	
Intestinal cancer [n (%)]	9 (24.3)	21 (48.8)	0.0366
Inflammatory bowel disease [n (%)]	4 (10.8)	1 (2.33)	0.18
Diverticular disease [n (%)]	9 (24.3)	19 (44.2)	0.0991
Complications (n (%)	18 (48.6)	11 (25.6)	0.0385
Age (years) [mean (SD)]	69.4 (14.3)	63.0 (14.9)	0.0674
No. of chronic conditions [(mean (SD)]	2.62 (2.06)	2.77 (2.46)	0.99
Operative time (minutes) [mean (SD)]	140.8 (70.6)	149.0 (79.8)	0.59

DRG = Diagnosis-Related Group; SD = standard deviation.

**P* values refer to Fisher's exact test for categorical variables and the rank-sum test for continuous variables.

†DRG codes refer to major small-bowel and large-bowel procedures. Code 329 includes major comorbid conditions, Code 330 refers to other comorbid conditions, and Code 331 refers to no comorbid conditions.

‡Surgery type was not available for one patient in the group not receiving alvimopan.

of the significance. Spearman correlations were used to compare continuous variables (e.g., age with outcomes).

For the multivariate analysis, we first performed a log transformation of our outcome variables to cause the data to be more normally distributed. We then used stepwise multiple linear regression to determine independent predictors of shorter times for the five outcome variables. Candidates for the stepwise multiple regressions were variables that yielded a *P* value of less than 0.15 in the univariate analysis. Results were considered significant when the *P* value was less than 0.05. We used SAS 9.2 for Windows (SAS Institute, Cary, N.C.) to perform all calculations.

RESULTS

Clinical Characteristics

Table 1 lists the patients' clinical characteristics according to drug status. The rate of drug utilization in the 329 DRG class was 7/(12+7) = 36.8%. The corresponding rate of drug use for class 330 patients was 40.6%, and the rate for class 331 was 79.3%. Thus, there was a significant increase in drug utilization ($P = 0.002$) as the DRG class became less complex as observed in the trend test.

The rate of drug use for open surgery was 15/(29+15) = 34.1%, which was significantly lower than the 80% rate for laparoscopy patients ($P < 0.0001$). Patients receiving alvimopan had significantly fewer complications compared with non-alvimopan patients (25.6% vs. 48.6% respectively; $P = 0.0385$). The alvimopan-treated patients were also significantly more likely to have a diagnosis of intestinal cancer compared with the non-drug group (48.8% vs. 24.3% respectively; $P = 0.0366$).

Univariate Analysis

Tables 2 through 10 provide descriptive statistics for the five outcome variables (by drug status, sex, DRG code, surgery type, cancer diagnosis, inflammatory bowel disease, diverticular disease, complications, age, number of chronic conditions, and operative time). Variables with a *P* value of less than 0.15 were used as candidates for the subsequent multivariate analysis.

Table 2 shows significantly shorter times ($P < 0.05$) for patients receiving alvimopan in all outcome variables except for the time to pass gas (almost significant at $P = 0.0551$). There were no significant differences in outcomes by sex (Table 3). Nonsignificance was also noted for diagnoses of cancer (Table 4) and diverticular disease (Table 5).

As noted in Table 6, the three DRG classes differed significantly from each other ($P < 0.05$, Tukey's test) for surgery to discharge LOS and for total LOS. Not unexpectedly for these two outcomes, LOS steadily increases as the DRG becomes increasingly complex.

Patients undergoing laparoscopic surgery, compared with those having open surgery, had significantly shorter times for all five outcome variables (Table 7; see page 522). Only five patients had inflammatory bowel disease. As shown in

Table 2 Descriptive Statistics of Outcome Variables by Drug Status

	Without Alvimopan (n = 37)			With Alvimopan (n = 43)			
Variable (Days)	***Mean***	***Median***	***SD***	***Mean***	***Median***	***SD***	***P* Value***
LOS–surgery to discharge	9.54	8.00	8.03	5.53	4.00	4.33	< 0.0001
Time to pass gas	2.19	2.00	1.94	1.55	1.00	0.75	0.0551
Time to liquid diet	3.30	3.00	1.79	2.26	2.00	1.16	0.0054
Time to solid diet	5.65	5.00	3.30	3.70	3.00	1.81	0.0008
Total LOS	13.50	11.00	10.60	6.42	5.00	4.40	< 0.0001

LOS = length of stay; SD = standard deviation.
**P* values refer to the rank-sum test.

Table 3 Descriptive Statistics of Outcome Variables by Sex

	Female (n = 45)			Male (n = 35)			
Variable (Days)	***Mean***	***Median***	***SD***	***Mean***	***Median***	***SD***	***P* Value***
LOS–surgery to discharge	6.96	6.00	5.06	7.69	4.00	8.27	0.38
Time to pass gas	2.04	2.00	1.80	1.59	2.00	0.79	0.26
Time to liquid diet	2.53	2.00	1.38	3.00	3.00	1.77	0.28
Time to solid diet	4.36	4.00	2.09	4.91	3.00	3.46	0.87
Total LOS	9.31	7.00	7.47	10.10	6.00	9.95	0.58

LOS = length of stay; SD = standard deviation.
**P* values refer to the rank-sum test.

Table 4 Descriptive Statistics of Outcome Variables by Intestinal Cancer

	No Cancer Diagnosis (n = 50)			Cancer Diagnosis (n = 35)			
Variable (Days)	***Mean***	***Median***	***SD***	***Mean***	***Median***	***SD***	***P* Value***
LOS–surgery to discharge	7.96	6.00	7.75	6.13	5.00	3.95	0.34
Time to pass gas	1.87	2.00	1.68	1.80	2.00	1.00	0.78
Time to liquid diet	2.76	3.00	1.42	2.70	2.00	1.80	0.54
Time to solid diet	4.76	4.00	2.90	4.33	4.00	2.56	0.53
Total LOS	10.80	7.00	10.00	7.83	6.00	5.02	0.20

LOS = length of stay; SD = standard deviation.
**P* values refer to the rank-sum test.

Table 8 (see page 522, however, these patients had significantly longer times for all outcomes except for time to pass gas ($P = 0.28$).

Patients with postsurgical complications had significantly longer times for all outcomes except for time to a liquid diet (almost significant at $P = 0.0507$) (Table 9; see page 522).

In Table 10 (see page 523), older age was significantly correlated with a longer time from surgery to discharge (Spearman $r = 0.24$; $P < 0.0349$) and with total LOS (Spearman $r = 0.31$; $P = 0.0056$).

Multivariate Analysis

The multivariate analysis is summarized in Table 11 (see page 523). All predictors with a P value of less than 0.15 in the univariate analysis were used as candidates for the stepwise multiple linear regression analysis. We used a cutoff of $P < 0.05$ to select variables for the final multivariate model.

Patients receiving alvimopan had significantly shorter times for all outcome variables except for time to a liquid diet. Although drug status was a significant predictor for time to a liquid diet in the univariate analysis ($P = 0.0054$) (see Table 2), it was not a factor in the multivariate model ($P = 0.18$).

Advanced age was a significant predictor only for longer total LOS, and open surgery was a significant predictor only for a longer time to a liquid diet. Inflammatory bowel disease and complications were independent predictors for longer times for three outcomes.

Finally, DRG status was a significant independent predictor of time from surgery to discharge and for total LOS. For both of these outcomes, patients with the most complex DRG code (329) had significantly longer GI recovery times than did patients with codes 330 and 331.

Except for time to a liquid diet, GI recovery times for our outcome variables (in days) were significantly reduced in patients using alvimopan. By taking the anti-log of the regression coefficients, we obtained a multivariate adjusted percentage change in the time reduction for each of our four significant outcome variables along with a 95% confidence interval (CI) (Table 12, page 524).

We provided descriptive statistics (medians) by drug status (see Table 2). Before the multivariate adjustments were made, the percentage of change in median times resulting from drug utilization ranged from –40% to –55%. After the multivariate adjustments, the model predicted that the changes were more modest (range, –22% to –29%; see Table 12). This was to be expected, because we adjusted for other significant predictors in the multivariate analysis (i.e., age, surgery type, inflammatory bowel disease, complications, and DRG status), and we had some confounding. Nevertheless, for all outcome variables (except time to a liquid diet), there was a reduction of about 25% (in days) for the alvimopan patients, as predicted by our multivariate models. This suggests that if the average LOS was 8 days, using alvimopan could reduce LOS by 2 days.

Prolonged Hospital Stays

Of the 43 patients who received alvimopan after undergoing laparoscopic or open-bowel resection, only three patients (7%) had a prolonged LOS (more than 10 days) from the time of surgery to the

Table 5 Descriptive Statistics of Outcome Variables by Diverticular Disease

	No Diverticular Disease (n = 52)			Diverticular Disease (n = 28)			
Variable (Days)	***Mean***	***Median***	***SD***	***Mean***	***Median***	***SD***	***P* Value***
LOS–surgery to discharge	7.37	5.00	6.94	7.11	5.00	6.10	0.85
Time to pass gas	1.86	1.00	1.69	1.82	2.00	0.90	0.40
Time to liquid diet	2.75	2.00	1.70	2.71	2.50	1.30	0.76
Time to solid diet	4.65	4.00	2.97	4.50	4.00	2.40	0.99
Total LOS	9.63	7.00	8.36	9.75	6.00	9.17	0.60

LOS = length of stay; SD = standard deviation.
*P values refer to the rank-sum test.

Table 6 Descriptive Statistics of Outcome Variables by Diagnosis-Related Group (DRG) Code

	Code 329 (n = 19)			Code 330 (n = 32)			Code 331 (n = 29)			
Variable (Days)	***Mean***	***Median***	***SD***	***Mean***	***Median***	***SD***	***Mean***	***Median***	***SD***	***P* Value***
LOS–surgery to discharge	14.00	11.00	10.50	6.19	6.00	2.81	4.07	4.00	1.36	<0.0001†
Time to pass gas	2.32	2.00	2.50	1.73	1.50	1.06	1.66	2.00	0.72	0.70
Time to liquid diet	3.26	3.00	1.52	2.88	2.00	1.81	2.24	2.00	1.15	0.0610
Time to solid diet	6.53	6.00	3.89	4.53	4.00	2.40	3.41	3.00	1.24	0.0030‡
Total LOS	17.70	13.00	13.20	8.81	7.00	5.10	5.38	5.00	2.13	<0.0001†

LOS = length of stay; SD = standard deviation.
DRG codes refer to major small-bowel and large-bowel procedures: code 329 = major comorbid conditions; code 330 = other comorbid conditions; code 331 = no comorbid conditions.
*P values refer to the Kruskal–Wallis test.
†Multiple comparison tests indicate that the three DRG groups differ significantly from each other ($P < 0.05$; Tukey's test).
‡Multiple comparison tests indicate that the DRG group 329 and the DRG group 331 differ significantly from each other ($P < 0.05$, Tukey's test).

time of hospital discharge (Table 13). The reasons for a prolonged LOS (average, 18 days) for these three patients included the development of pleural effusion, blood clots, and GI bleeding.

Of the 37 individuals who did not receive alvimopan after laparoscopic or open-bowel resection, 11 patients (29.7%) had a prolonged LOS (more than 10 days) from the time of surgery to the time of discharge (see Table 13). The prolonged LOS for the 11 patients was attributed to pain management, infection, bleeding complications, an elevated International Normalized Ratio, desaturation and hypoxemia, perioperative myocardial injury, fluid overload, sepsis, urinary retention, aspiration pneumonia, tachycardia, congestive heart failure, respiratory failure, pleural effusion, atrial fibrillation, and cardiac complications. One patient who did not receive alvimopan was undergoing an additional procedure (cystoscopy, bilateral ureteral catheter insertion, or partial cystectomy). The average prolonged LOS for the 11 patients was 18 days (see Table 13 on page 524).

Table 7 Descriptive Statistics of Outcome Variables by Surgery Type

	Laparoscopic (n = 35)			Open Surgery (n = 44)			
Variable (Days)	***Mean***	***Median***	***SD***	***Mean***	***Median***	***SD***	***P* Value***
LOS–surgery to discharge	4.97	4.00	2.93	9.18	7.00	8.09	0.0002
Time to pass gas	1.50	1.00	0.68	2.14	2.00	1.82	0.0495
Time to liquid diet	2.06	2.00	1.08	3.32	3.00	1.67	0.0002
Time to solid diet	3.74	3.00	2.19	5.32	5.00	3.02	0.0017
Total LOS	6.71	5.00	4.62	12.00	9.00	10.30	0.0002

LOS = length of stay; SD = standard deviation.
**P* values refer to the rank-sum test.

Table 8 Descriptive Statistics of Outcome Variables by Inflammatory Bowel Disease (IBD)

	No IBD Diagnosis (n = 75)			IBD Diagnosis (n = 5)			
Variable (Days)	***Mean***	***Median***	***SD***	***Mean***	***Median***	***SD***	***P* Value***
LOS–surgery to discharge	6.43	5.00	4.65	20.00	12.00	15.8	0.0037
Time to pass gas	1.83	2.00	1.49	2.00	2.00	0.71	0.28
Time to liquid diet	2.63	2.00	1.53	4.40	4.00	1.14	0.0094
Time to solid diet	4.35	4.00	2.40	8.40	7.00	5.03	0.0117
Total LOS	8.59	7.00	6.60	26.00	23.00	17.2	0.0048

LOS = length of stay; SD = standard deviation.
**P* values refer to the rank-sum test.

Table 9 Descriptive Statistics of Outcome Variables by Complications

	No Complications (n = 51)			Complications (n = 29)			
Variable (Days)	***Mean***	***Median***	***SD***	***Mean***	***Median***	***SD***	***P* Value***
LOS–surgery to discharge	4.49	4.00	1.72	12.2	9.00	8.90	< 0.0001
Time to pass gas	1.75	1.00	1.69	2.00	2.00	0.93	0.0200
Time to liquid diet	2.47	2.00	1.39	3.21	3.00	1.76	0.0507
Time to solid diet	3.67	3.00	1.47	6.24	6.00	3.66	0.0003
Total LOS	6.12	5.00	2.53	15.90	13.00	11.50	< 0.0001

LOS = length of stay; SD = standard deviation.
**P* values refer to the rank-sum test.

DISCUSSION

Postoperative ileus (POI) after bowel resection occurs frequently and can cause severe discomfort. POI leads to increased LOS and higher health care costs. Alvimopan (Entereg) was approved by the FDA to improve recovery time in the GI tract after small-bowel or large-bowel resection with primary anastomosis to prevent POI.[5–7] In our literature search, several articles showed the clinical and economic benefits of alvimopan in reducing the number of days needed for GI recovery and for decreasing health care costs associated with POI.

In a retrospective cohort study, 480 bowel-resection surgery patients who received alvimopan were compared with 960 matched placebo controls.[6] An average of $1,040 ($P = 0.033$) was saved by using alvimopan. The mean LOS was 6.5 days for controls and 5.6 days for alvimopan-treated patients ($P < 0.001$).

In a 6-month, open-label, multihospital prospective study, 108 alvimopan patients had a mean shorter postoperative LOS of 1.8 days ($P = 0.01$) and lower rates of nasogastric tube insertion compared with 91 control patients (2% vs. 15%, respectively; $P < 0.001$).[8] Further analysis revealed a statistically significant reduction in postoperative LOS of approximately 1.2 days ($P = 0.01$) in the alvimopan group, regardless of age or surgery type, with an even larger difference (3.2 days) observed in patients older than 70 years of age. As in the retrospective cohort study by Poston et al.,[6] an economic benefit was associated with alvimopan, ranging from $531 per patient for laparoscopic bowel resection to $997 per patient for open-bowel resection.[3,8]

In a German trial, 738 patients underwent open abdominal surgery. Alvimopan was more effective for those who used patient-controlled analgesia (PCA) than for patients who did not use it. Alvimopan was well tolerated and did not reverse analgesia.[9]

A pool of three other trials by Delaney et al. showed that

Table 10 Correlation of Age, Chronic Conditions, and Operative Time With Outcome Variables

	Age		No. of Chronic Conditions		Operative Time	
Outcome Variable	***r* Value**	***P* Value**	***r* Value**	***P* Value**	***r* Value**	***P* Value**
LOS–surgery to discharge	0.24	0.0349*	0.12	0.29	0.19	0.0856†
Time to pass gas	0.09	0.45	0.10	0.39	0.07	0.54
Time to liquid diet	0.00	0.97	0.01	0.90	0.15	0.18
Time to solid diet	0.12	0.27	0.10	0.37	0.10	0.38
Total LOS	0.31	0.0056*	0.14	0.23	0.21	0.0616†

r value = Spearman correlation coefficient.
*$P < 0.05$.
†$0.05 < P < 0.10$.
LOS = length of stay.

alvimopan significantly accelerated GI recovery time ($P \leq 0.001$) and significantly reduced hospital LOS.[10] Alvimopan-treated patients also had significantly accelerated GI recovery times ($P < 0.001$). Tolerability profiles were similar among the alvimopan and placebo groups.

In a similar primary endpoint trial by Ludwig et al., alvimopan was well tolerated and prominently accelerated GI-2 recovery (toleration of solid food and first bowel movement), GI-3 recovery (toleration of solid food and either first flatus or bowel movement), and actual hospital discharge, compared with a standardized accelerated postoperative care pathway alone ($P < 0.001$ for all).[11]

Table 11 Significant Predictor *P* Values ($P < 0.05$) for Multivariate Analysis

Predictor	LOS–Surgery to Discharge	Time to Pass Gas	Time to Liquid Diet	Time to Solid Diet	Total LOS
Drug status	0.0077	0.0330	—	0.0184	0.0010
Age	—	—	—	—	0.0440
Type of Surgery	—	—	0.0003	—	—
IBD	0.0297	—	0.0334	—	0.0095
Complications	< 0.0001	—	—	0.0020	< 0.0001
DRG Status					
329 vs. 330	0.0019	—	—	—	0.0385
329 vs. 331	0.0007	—	—	—	0.0081
Total *r*-square (%)	0.6450	0.0570	0.2195	0.2137	0.6359

DRG = Diagnosis-Related Groups; IBD = inflammatory bowel disease; LOS = length of stay.

A non-blank cell of the table (except for the last line) indicates variables remaining in the multivariate models as significant predictors for particular outcome variables; the cell entry is the significant *P* value ($P < 0.05$).

The last line of the table indicates the total percentage of variation explained by the significant predictor variables for each outcome variable (total *r*-square).

This table contains only predictors that were significant ($P < 0.05$) in the multivariate analysis and thus remained in the final model for at least one outcome. All other parameters do not appear (i.e., sex, intestinal cancer, diverticular disease, number of chronic conditions, and operative time).

Four U.S. studies and the German randomized, double-blind, parallel-group, placebo-controlled study were cumulatively analyzed.[4] In these studies, GI-2 was preferred over GI-3 because it represented a more clinically relevant treatment response to the resection procedure.[4] GI recovery time was consistently shorter with alvimopan than with placebo, and alvimopan achieved GI-2 more rapidly than placebo. Full recovery time ranged from 92 to 116.4 hours with alvimopan, compared with a recovery time of 109.5 to 132 hours with placebo.[4]

Alvimopan has the ability to accelerate recovery of the upper or lower GI tract after partial large-bowel or small-bowel resection with primary anastomosis. This opioid drug is limited to institutional use and is approved for a maximum administration time of 7 days. Because many patients receive opioid medications during hospital stays, alvimopan is contraindicated in patients who received therapeutic doses of opioids for 7 consecutive days before surgery.

The major goals of these studies of alvimopan were to decrease hospital LOS and to shorten the time to preset markers of GI recovery. As with these studies, our primary goal was to confirm, using a multivariate analysis, that LOS (the time from surgery to hospital discharge) was shorter for patients treated with alvimopan than for patients who did not receive the drug.

DRG codes also proved influential in our analysis. Class 329 patients (those with the most complicated cases) had longer recovery times compared with patients in either DRG 330 or DRG 331. Thus, DRG was found to play a role in outcomes.

The patient's age and sex did not influence this variable. We evaluated age because it had been suggested that age might affect recovery time after bowel resection. In the retrospective study of alvimopan, Poston et al. divided patients into four subgroups according to age and evaluated LOS in alvimopan users and non-users.[6] Johnson and Walsh reviewed therapies for shortening the duration of POI and found, through a pooled analysis of phase 3 studies of alvimopan, that the 12-mg dose was more beneficial than a 6-mg dose after bowel resection, especially in women and in patients older than 65 years of age.[12] For this reason, we considered patients' ages when evaluating outcomes.

In our final multivariate analysis, we concluded that alvimopan significantly reduced all outcome times (except for time to a liquid diet), even after we accounted for patient demographics, DRG status, type of surgery, complications,

Table 12 Univariate and Multivariate Adjusted Percentage Decreases in Outcome Measures by Drug Status

Outcome	Median (Days) Without Alvimopan	Median (Days) With Alvimopan	Percent Change in Medians	Multivariate-Adjusted Percentage Change (95% CI)
LOS–surgery to discharge	8.00	4.00	–50.0	–23.0 (–36.3 to –6.87)
Time to pass gas	2.00	1.00	–50.0	–22.0 (–38.0 to –20.5)
Time to solid diet	5.00	3.00	–40.0	–24.0 (–39.5 to –4.65)
Total LOS	11.00	5.00	–55.0	–29.4 (–42.3 to –13.6)

LOS = length of stay; CI = confidence interval.

comorbidities, and operative time.

Many clinical trials have been performed to evaluate the efficacy of alvimopan in accelerating GI recovery after bowel surgery. The purpose of our study was to obtain information about our institution's experience with the drug. Our results agreed with the FDA's position that alvimopan could be used to reduce the time to GI recovery following bowel resection.

In the prescribing information for alvimopan, GI-2 recovery is described as the time to toleration of solid food and the first bowel movement after surgery.[4] In five multicenter, randomized, double-blind studies that were conducted to assess GI-2 recovery time, the average relative risk reduction was 14% (range, 10%–20%) for patients receiving alvimopan. Our study looked at GI-2 recovery time as well, described as time to a solid diet (see Table 2). We found a 31% relative risk reduction (5.65 days vs. 3.7 days, respectively). Our study also compared LOS among patients who received alvimopan with LOS among those who did not. This endpoint was not evaluated by the studies cited in the prescribing information.[4]

Poston et al. reported a 14% relative reduction in LOS for patients who received alvimopan compared with patients who did not.[6] After multivariate adjustments were made (see Table 12), our models predicted a 24% reduction in time to a solid diet for alvimopan patients compared with non-alvimopan patients. We found a 29.4% reduction in total LOS for alvimopan compared with placebo. We therefore confirmed the findings of Poston et al. in regard to LOS.

STUDY LIMITATIONS

Our retrospective study was limited by the small sample size and by a heterogeneous patient population. As with all retrospective studies, we were able to control for a limited number of known factors (age, type of surgery, inflammatory bowel disease, complications, DRG status, sex, intestinal cancer, diverticular disease, chronic conditions, and operative time). Other unknown confounding variables might have differed between the alvimopan and non-alvimopan groups. Our results should be confirmed in large, randomized trials.

More than 20 surgeons participated in this study, which might account for some of the discrepancies reported for patients' postsurgical recovery times.

More patients receiving alvimopan underwent laparoscopy (65%), which is less invasive than open surgery, compared with non-alvimopan patients (19.4%). Patients undergoing invasive open surgery would be expected to have a longer LOS than patients undergoing laparoscopic surgery.

Patients' DRG classifications were not evenly dispersed between the alvimopan and non-alvimopan groups. In the alvi-

Table 13 Prolonged Hospital Length of Stay (LOS)

Alvimopan Patient No.	LOS From Surgery Day to Discharge (Days)	Comment
1	11	Development of low-grade fever and pleural effusion
2	28	Development of blood clot
3	15	Development of active gastrointestinal bleeding
Non-Alvimopan Patient No.	**LOS From Surgery Day to Discharge (Days)**	**Comment**
1	10	Pain management and infection
2	15	Patient underwent concomitant procedures (cystoscopy, bilateral ureteral catheter insertion, partial cystectomy)
3	10	Elevated International Normalized Ratio
4	10	Desaturation, hypoxemia
5	12	Extensive bleeding
6	28	Small perioperative myocardial injury, fluid overload, sepsis, urinary retention
7	12	Aspiration pneumonia
8	11	Tachycardia, congestive heart failure
9	25	Cardiac complications, myocardial infarction
10	18	Atrial fibrillation
11	44	Pleural effusion and respiratory failure

mopan group, only 16.3% of patients were classified as having the most complicated cases (DRG 329), compared with 32.4% of the non-alvimopan group. Conversely, 53.5% of the alvimopan-treated patients were classified as having the least complicated cases (DRG 331), compared with 16.2% in the non-alvimopan group. Using multivariate analysis, we attempted to control for these baseline differences.

CONCLUSION

Patients who received alvimopan after bowel surgery had shorter times to GI recovery ($P < 0.05$) compared with patients who did not receive this drug, even after adjustments were made for DRG status, type of surgery, complications, comorbidities, and operative time. Alvimopan improved the quality of surgical care and reduced the cost of such care. We found alvimopan to be a good choice for the perioperative management of patients undergoing segmental bowel resection with primary anastomosis.

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