Bladder | **2015** | Vol. 2(1) | e11
DOI: 10.14440/bladder.2015.48

RESEARCH ARTICLE

# Clinical utilization patterns of alvimopan in a contemporary cohort of patients undergoing radical cystectomy

Pranav Sharma*, John S Fisher, Kamran Zargar-Shoshtari, Scott M Gilbert, Julio M Pow-Sang, Wade J Sexton, Philippe E Spiess, Michael A Poch

Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, FL, USA

* Corresponding author: Pranav Sharma, MD, Genitourinary Oncology Fellow, H. Lee Moffitt Cancer Center, 12902 Magnolia Dr. Tampa, FL 33612. Tel: (813) 745-8814, Fax: (813) 745-8494, E-mail: pranav.sharma@moffitt.org

Competing interests: The authors have declared that no competing interests exist.

Abbreviations used: AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; BC, bladder cancer; BM, bowel movement; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CV, cardiovascular; EBL, estimated blood loss; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ERAS, enhanced recovery after surgery; ESLD- end-stage liver disease; ESRD, end-stage renal disease; FDA, Food and Drug Administration; GI, gastrointestinal; IQR, interquartile range; IRB, Institutional Review Board; LND, lymphadenectomy; LOS, length of stay; MI, myocardial infarction; MVAC, methotrexate, vinblastine, adriamycin, cisplatin; NGT, nasogastric tube; OR, operating room; PCI, percutaneous coronary intervention; PLND, pelvic lymph node dissection; PMH, past medical history; pN, pathologic nodal classification; POI, postoperative paralytic ileus; PSH, past surgical history; pT, pathologic tumor classification; RC, radical cystectomy; RCT, randomized clinical trial; SBO, small bowel obstruction; SPSS, Statistical Package for the Social Sciences; TAH, total abdominal hysterectomy; TPN, total parenteral nutrition; TUR, transurethral resection; XRT, radiation

Received March 23, 2015; Revision received April 16, 2015; Accepted April 17, 2015; Published April 22, 2015

## ABSTRACT

**OBJECTIVE:** To evaluate the clinical utilization patterns and outcomes of alvimopan, a peripherally-acting μ-opioid receptor antagonist, after radical cystectomy (RC) and urinary diversion at a high-volume cancer center.

**PATIENTS AND METHODS:** We retrospectively identified 130 consecutive patients who underwent RC and urinary diversion for bladder cancer at our institution from October 2013 to September 2014. Demographic, clinical, and post-operative outcomes were compared between patients who did and did not receive alvimopan using the Kruskal-Wallis test for medians and the chi-square test for proportions. Predictors of 30-day complications and prolonged length of stay (LOS) were analyzed using multivariate logistic regression analysis.

**RESULTS:** Perioperative alvimopan was given to 81 patients (62.3%) during the study period although in 17 patients (13.1%) it was indicated but not given. The most common absolute or relative contraindication for alvimopan usage was prior consumption of opioids for more than 7 consecutive days (n = 18; 13.8%). Patients who received alvimopan had a better performance status ($P$ = 0.06), less comorbidities ($P$ = 0.08), and were more likely to have minimally-invasive surgery ($P$ = 0.07) although these differences did not reach statistical significance. Alvimopan usage was independently associated with less postoperative 30-day complications (odds ratio [OR]: 0.35, 95% confidence interval [CI]: 0.15–0.82; $P$ = 0.015), less high-grade complications (OR: 0.12, 95% CI: 0.044–0.34; $P$ < 0.01), and less prolonged hospitalization > 10 days (OR: 0.28, 95% CI: 0.11–0.72; $P$ = 0.008).

**CONCLUSIONS:** Despite its clinical benefits, alvimopan was under-utilized in RC patients, especially in those with worse baseline health. We recommend its incorporation into standardized protocols to optimize perioperative care.

**Keywords:** alvimopan, enhanced recovery, fast track, ileus, radical cystectomy

## INTRODUCTION

Radical cystectomy (RC) and urinary diversion is the preferred treatment for muscle-invasive bladder cancer (BC) [1]. Since it is associated with bowel resection and reconstruction, postoperative paralytic ileus (POI) can occur with an incidence ranging from 1.58% to 23.5% [2]. Delayed gastrointestinal (GI) recovery can also lead to a longer hospital stay and increased risk of postoperative complications [3,4].

Alvimopan is a peripherally acting μ-opioid receptor antagonist that counteracts the effects of perioperative pain medication in the GI tract. It was initially reported to accelerate the recovery of bowel function in patients undergoing partial colectomy or total abdominal hysterectomy (TAH) [5]. In October 2013, the US Food and Drug Administration (FDA) expanded its indication to patients undergoing RC and urinary diversion based on the results of a multi-institutional randomized clinical trial (RCT) [6]. In this prospective study, alvimopan hastened bowel recovery by a median of 1.2 days and shortened median length of stay (LOS) by 1 day. Prolonged (> 7 days) LOS and POI-related morbidity

were also reduced by 18–20%.

The purpose of our study was to evaluate the utilization patterns and outcomes of alvimopan in BC patients treated with RC at a high-volume cancer center during the first year after FDA approval. Our primary objective was to determine whether alvimopan usage reduced postoperative complications, high-grade complications, and minimized prolonged hospitalization after surgery in a non-trial population in order to reestablish its effectiveness.

## PATIENTS AND METHODS

### Data source

The study cohort consisted of 130 patients with BC treated with RC and urinary diversion consecutively between October 2013 and September 2014 by five different surgeons. One patient was excluded secondary to a cutaneous ureterostomy urinary diversion, and no patient had known distant metastatic disease prior to surgery.

Patients were identified in an Institutional Review Board (IRB)-approved departmental database, which retrospectively abstracts all demographic information, clinical data, and postoperative follow-up on patients that undergo RC at Moffitt Cancer Center. It is updated by on a daily basis by dedicated departmental data analysts, and follow-up is maintained through postoperative clinical notes.

### Alvimopan utilization

All patients were eligible for alvimopan since intravenous opioid-based patient-controlled analgesia (morphine or dilaudid) was routinely given postoperatively as part of our perioperative care pathway. Most patients did not receive epidural anesthesia, but non-steroidal anti-inflammatory agents (ketorolac or cyclooxygenase-2 inhibitors) were routinely used. Nasogastric tube (NGT) decompression was discontinued at the end of surgery and not routinely utilized in the postoperative period. Oral feeding was resumed on postoperative day 2 in all patients with a clear liquid diet, and it was advanced to a soft, surgical diet on postoperative day 3 if the patient was tolerating liquids appropriately. Standardized enhanced recovery after surgery (ERAS) or fast-track protocols, however, were not utilized.

Alvimopan was dosed at 12 mg and was given orally between 30 minutes and 2 hours before surgery as well as twice daily postoperatively until hospital discharge or for a maximum of 7 days (15 in-hospital doses). Clinical reasons that prevented alvimopan usage were based on the "Contraindications" and the "Warnings and Precautions" label in the prescribing information section of the drug's main website at www.entereg.com. These were subsequently categorized into 1) prior opioid use for more than 7 consecutive days, 2) prior cardiac condition such as coronary artery disease (CAD), arrhythmia, or valvular disease requiring percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), pacemaker/defibrillator placement, or valve replacement, 3) end-stage renal disease (ESRD), 4) end-stage liver disease (ESLD), 5) pre-existing partial or complete small bowel obstruction (SBO), 6) prior pancreatic or gastric anastomosis, or 7) known allergy to the drug. Patients not given alvimopan were identified retrospectively and the indication for non-use was determined from the patient's past medical history (PMH) and clinical status before surgery. Patients with multiple reasons for non-use were assigned the one considered the most severe. Patients who were appropriate candidates for alvimopan (without an absolute or relative contraindication as listed above) but did not receive the drug were documented as "indicated, not received."

### Study variables

Study variables included patient demographics (age, gender and race), smoking status, body mass index (BMI), history of prior abdominal surgery, Eastern Cooperative Oncology Group (ECOG) performance status, age-adjusted Charlson Comorbidity Index (CCI), and American Society of Anesthesiologists (ASA) score. BMI was based on the patient's height and weight at the time of surgery, past surgical history (PSH), PMH, and ECOG performance status were identified during the patient's last preoperative clinic visit within 2 months of RC, ASA score was determined by the anesthesiologist's assessment of the patient two to three hours before surgery, and CCI was derived from the patient's PMH. Preoperative albumin and creatinine levels were also obtained from solitary measurements drawn 1 to 2 weeks prior to surgery.

Disease-specific characteristics included clinical tumor histology during most recent transurethral resection (TUR), use of neoadjuvant chemotherapy, history of prior pelvic radiation (XRT) therapy, and pathologic tumor (pT) and nodal (pN) classification. All outside histology slides were re-reviewed by our institution's pathologists with expertise in genitourinary malignancy, and staging was assigned according to the 2010 American Joint Committee on Cancer system (AJCC).

Intraoperative factors included surgical approach, type of urinary diversion, extent of lymphadenectomy (LND), median operative time, and median estimated blood loss (EBL) during surgery. RC was performed with either an open or robotic-assisted laparoscopic approach at our institution, and the extent of pelvic lymph node dissection (PLND) was defined as limited (obturator nodes), standard (obturator, internal, and external iliac nodes), or extended (obturator, internal, external, and common iliac nodes).

Short-term postoperative outcomes included time to first passage of flatus and bowel movement (BM), development of POI, use of total parenteral nutrition (TPN), LOS, and presence of 30-day complications including death. Return of bowel function was abstracted from daily progress notes, which were standardized to include this measure as a required data element for documentation. POI was defined as the inability to tolerate an oral liquid or solid diet associated with abdominal distention on physical examination after a minimum of 7 days. TPN was utilized in patients who were unable to tolerate anything by mouth for a minimum of 7–10 days, and LOS was defined from the date of surgery until the date of initial discharge. Complications were captured via retrospective chart review of the patient's postoperative course (i.e. discharge summary) and subsequent clinic visits up to 30 days after RC. The Clavien-Dindo scoring system was used to categorize 30-day complications, and patients with multiple complications during the postoperative period were assigned the one with the highest grade. High-grade complications were defined as Clavien ≥ IIIa, and the 30-day mortality rate was recorded.

### Statistical Analysis

Continuous variables were reported as medians and interquartile ranges (IQRs), and categorical variables were reported as frequency

counts and percentages. Clinicodemographic characteristics, pathological features, and postoperative outcomes were compared for patients treated with and without alvimopan. We used the Kruskal-Wallis test to determine any differences in medians, and the chi-square test for proportions. Multivariable logistic regression analysis was used to determine the association of relevant demographic, clinical, and pathological features with our three primary outcomes of: 1) any postoperative 30-day complication regardless of Clavien score, 2) any high-grade complication within 30 days of surgery, and 3) prolonged LOS > 10 days, which represented the uppermost quartile in the study population. Clinically significant variables (pT stage, alvimopan usage) were included in the adjusted multivariate model as well as any variable that was significantly different between groups on univariate analysis ($P < 0.1$).

Statistical analyses was performed with the Statistical Package for the Social Sciences (SPSS) software package version 21.0 (IBM Corporation, Armonk, NY). All tests were 2-sided with a p-value < 0.05 considered as statistically significant.

## RESULTS

### Clinicopathological characteristics

The demographic, clinical, and pathological characteristics of our study population are listed in **Table 1**. Patients who received alvimopan, in general, were healthier with a better ECOG performance status ($P = 0.06$) and less comorbidities ($P = 0.08$) than patients who did not although these differences did not reach statistical significance. Patients who were candidates for alvimopan but did not receive the drug had a lower median preoperative creatinine ($P = 0.08$), but this difference also did not reach statistical significance.

The majority of patients treated with neoadjuvant chemotherapy received gemcitabine and cisplatin (n = 44; 33.8%). Four patients received gemcitabine and carboplatin (3.1%), three received methotrexate, vinblastine, adriamycin, cisplatin (MVAC) (2.3%), and one received gemcitabine and taxotere (0.8%). The median number of cycles given was 3 (IQR: 3–4).

### Intraoperative and postoperative outcomes

The intraoperative and postoperative outcomes of our study population are listed in **Table 2**. Patients who received alvimopan were more likely to have robotic-assisted radical cystectomy (RARC) ($P = 0.07$) although this difference did not reach statistical significance.

The overall 30-day postoperative complication rate in our study cohort was 58.5% (n = 76). Twenty-seven patients (20.8%) experienced a high-grade complication after surgery, and the 30-day mortality rate was 2.3% (3 deaths).

### Alvimopan outcomes

Eighty-one patients (62.3%) received perioperative alvimopan during the study period. Seventeen patients (13.1%) who did not receive alvimopan were candidates for therapy with no known absolute or relative contraindications to the drug. When combined with patients who actually received alvimopan, a total of 98 patients (75.4%) were eligible for treatment in our study population. The most common absolute or relative contraindication to therapy was prior opioid use for more than seven consecutive days (n = 18; 13.8%) followed by a PMH of cardiac disease (n = 12; 9.2%) (**Table 3**).

Patients treated with alvimopan had a quicker median time to first flatus ($P = 0.007$) and BM ($P < 0.01$), less POI ($P < 0.01$), decreased use of TPN ($P < 0.01$), shorter LOS ($P < 0.01$), and fewer 30-day complications after surgery ($P < 0.01$), including high-grade complications ($P < 0.01$) (**Table 2**). A sub-analysis of patients who underwent RARC also showed similar outcomes with the use of alvimopan with shorter median time to first flatus (3 vs. 5 days) and BM (5 vs. 6 days) and reduced LOS (6 vs. 7 days) although this analysis was limited by small numbers that are underpowered since only 16 patients (12.3%) underwent RARC.

On multivariate analysis when accounting for performance status, patients comorbidities, preoperative renal function, type of surgical approach, and tumor stage, alvimopan usage was independently associated with less postoperative 30-day complications (odds ratio [OR]: 0.35, 95% confidence interval [CI]: 0.15–0.82; $P = 0.015$) (**Table 4**), less high-grade complications (OR: 0.12, 95% CI: 0.044–0.34; $P < 0.01$) (**Table 5**), and less prolonged hospitalization > 10 days (OR: 0.28, 95% CI: 0.11–0.72; $P = 0.008$) (**Table 6**).

## DISCUSSION

As seen in a recent RCT, alvimopan was associated with improved bowel recovery, shorter hospital stay, and reduced postoperative 30-day complications after RC and urinary diversion in patients with BC [6]. It counteracts the effects of opioids in the gut thus preventing the development of delayed GI transit.

Our study confirms similar findings in a contemporary clinical setting. Median time to first BM with alvimopan was 5 days, similar to the 4.9 days reported by the RCT, and it was 6 days without alvimopan, comparable to the 6.1 days in the placebo arm. Postoperative LOS was similar to that reported in the RCT (6 vs. 7 days in alvimopan group, 8 vs. 8 days in non-alvimopan group), and use of TPN was comparable based on the reported phase IV data (3.7 vs. 10% in alvimopan group, 22.4 vs. 25% in non-alvimopan group) [7]. Additionally, our patient population was similar to that of the RCT, being predominately white males who were current or former smokers, and the distribution of surgical approaches for RC (i.e. open vs. robotic), operative times, and EBL were comparable.

Due to the above findings, we can conclude that the perioperative care in our study population is somewhat reflective of standardized management algorithms in larger, prospective studies. Our group was less likely to receive an orthotopic neobladder or a continent cutaneous urinary diversion compared to the RCT cohort (10 vs. 38.2% and 4.6 vs. 10.7%, respectively), but this difference may be indicative of the older patient population seen in our study (mean 69.2 vs. 65 years).

One of the limitations of the RCT is its applicability to only a highly-selected group of patients within the confines of pre-defined inclusion and exclusion criteria. Lee at al. did not comment on how many screened patients were excluded from the study and why these patients did not qualify for randomization [6]. Our objective was to identify current clinical practice patterns and outcomes of alvimopan use at a high-volume cancer center and determine why patients did not receive the drug in an appropriately indicated surgical setting.

Alvimopan was not maximally utilized in our study population with 81 out of 98 eligible patients receiving treatment (82.7%). Thirty-two patients (24.6%) had an identified absolute or relative contraindication to therapy, most commonly due to prior chronic opioid use followed by a PMH of underlying cardiovascular (CV) disease.

**Table 1. Demographic, clinical, and pathological characteristics.**

| | Total (n = 130) | Alvimopan (n = 81) | No alvimopan (n = 32) | Alvimopan indicated but not received (n = 17) | P-value |
|---|---|---|---|---|---|
| Median age at RC, years (IQR) | 70.1 (62.6–76.1) | 69.9 (62.1–75.7) | 70.4 (63.5–77.3) | 67.9 (61.7–75.3) | 0.95 |
| Sex, no. (%) | | | | | 0.41 |
| Male | 94 (72.3) | 60 (74.1) | 24 (75.0) | 10 (58.8) | |
| Female | 36 (27.7) | 21 (25.9) | 8 (25.0) | 7 (41.2) | |
| Race, no. (%) | | | | | 0.22 |
| White | 122 (93.8) | 78 (96.3) | 28 (87.5) | 16 (94.1) | |
| Non-white | 8 (6.2) | 3 (3.7) | 4 (12.5) | 1 (5.9) | |
| Smoking (current or former), no. (%) | 103 (79.3) | 63 (77.8) | 27 (84.4) | 13 (76.5) | 0.71 |
| Median BMI, kg/m$^2$ (IQR) | 27.6 (24.7–30.9) | 27.6 (24.8–31.9) | 26.9 (23.7–29.8) | 27.2 (24.7–30.9) | 0.43 |
| Prior abdominal surgery, no. (%) | 54 (41.5) | 34 (42.0) | 13 (40.6) | 7 (41.2) | 0.99 |
| ECOG Performance Status, no. (%) | | | | | 0.06 |
| 0 | 88 (67.7) | 61 (75.3) | 18 (56.3) | 9 (52.9) | |
| 1–2 | 42 (32.3) | 20 (24.7) | 14 (43.8) | 8 (47.1) | |
| Age-adjusted CCI, no. (%) | | | | | 0.08 |
| 2–6 | 72 (55.4) | 51 (63.0) | 13 (40.6) | 8 (47.1) | |
| ≥ 7 | 58 (44.6) | 30 (37.0) | 19 (59.4) | 9 (52.9) | |
| ASA score, no. (%) | | | | | 0.15 |
| 2 | 62 (47.7) | 44 (54.3) | 12 (37.5) | 6 (35.3) | |
| 3–4 | 68 (52.3) | 37 (45.7) | 20 (62.5) | 11 (64.7) | |
| Clinical histology, no. (%) | | | | | 0.12 |
| Pure UC | 84 (64.6) | 51 (63.0) | 25 (78.1) | 8 (47.1) | |
| UC variants | 41 (31.5) | 28 (34.6) | 6 (18.8) | 7 (41.2) | |
| Non-UC | 5 (3.8) | 2 (2.5) | 1 (3.1) | 2 (11.8) | |
| Median pre-op albumin, g/dL (IQR) | 4.1 (3.9–4.3) | 4.1 (3.9–4.3) | 4.1 (4.0–4.3) | 4.0 (3.9–4.2) | 0.43 |
| Median pre-op creatinine, mg/dL (IQR) | 1.0 (0.8–1.2) | 1.0 (0.9–1.2) | 1.0 (0.9–1.2) | 0.9 (0.7–1.0) | 0.08 |
| Neoadjuvant chemotherapy, no. (%) | 52 (40.0) | 34 (42.0) | 13 (40.6) | 5 (29.4) | 0.63 |
| Previous pelvic XRT, no. (%) | 15 (11.5) | 9 (11.1) | 4 (12.5) | 2 (11.8) | 0.98 |
| Pathologic T stage, no. (%) | | | | | 0.21 |
| T0–T1 | 49 (37.7) | 34 (42.0) | 12 (37.5) | 3 (17.6) | |
| T2 | 20 (15.4) | 11 (13.6) | 7 (21.9) | 2 (11.8) | |
| T3–T4 | 61 (46.9) | 36 (44.4) | 13 (40.6) | 12 (70.6) | |
| Pathologic N stage, no. (%) | | | | | 0.42 |
| N0 | 101 (77.7) | 63 (77.8) | 23 (71.9) | 15 (88.2) | |
| N+ | 29 (22.3) | 18 (22.2) | 9 (28.1) | 2 (11.8) | |

The utilization of alvimopan only in patients without significant cardiac conditions, however, has recently come into question. Although there were more reported myocardial infarctions (MIs) in patients treated with alvimopan 0.5 mg twice daily compared to placebo in a 12-month study of patients on chronic opioids for non-cancer pain, this has not been observed in the surgical setting [8,9]. Phase III trials in the patients undergoing bowel resection or TAH have shown similar CV toxicity profiles in alvimopan compared to placebo [10-12]. In the RC population, alvimopan had a similar CV risk to that of placebo with a lower number of postoperative adverse CV events (8.4 vs. 15.3%) including MI (2.8 vs. 7.3%) and a similar number of electrocardiogram (ECG) procedures needed on phase IV analysis (130 vs. 126, $P = 0.327$). In our study, there was no difference in the incidence of postoperative 30-day cardiac complications in patient who did and did not receive alvimopan (4.9 vs. 10.2%, $P = 0.30$) although this comparison is confounded since patients with underlying CV disease or comorbidities were pre-selected

to not receive the drug. If history of a cardiac condition was not a relative contraindication to alvimopan use, a total of 110 patients (84.6%) would have been eligible for therapy, and the overall utilization rate would have been 73.6%. We, therefore, advocate dropping CV disease as an exclusion criterion for alvimopan use and avoid restricting use in patients with cardiac history in order to maximize patient benefit from treatment.

**Table 2. Intraoperative and postoperative outcomes.**

| | Total (n = 130) | Alvimopan (n = 81) | No alvimopan (n = 32) | Alvimopan indicated but not received (n = 17) | P-value |
|---|---|---|---|---|---|
| Surgical approach, no. (%) | | | | | 0.07 |
| Open | 114 (87.7) | 67 (82.7) | 30 (93.8) | 17 (100.0) | |
| Robotic-assisted | 16 (12.3) | 14 (17.3) | 2 (6.3) | 0 (0.0) | |
| Urinary diversion, no. (%) | | | | | 0.46 |
| Ileal conduit | 111 (85.4) | 70 (86.4) | 27 (84.4) | 14 (82.4) | |
| Neobladder | 13 (10.0) | 6 (7.4) | 5 (15.6) | 2 (11.8) | |
| Continent cutaneous pouch | 6 (4.6) | 5 (6.2) | 0 (0.0) | 1 (5.9) | |
| Lymphadenectomy, no. (%) | | | | | 0.14 |
| Limited/Standard | 32 (24.6) | 17 (21.0) | 12 (37.5) | 3 (17.6) | |
| Extended | 98 (75.4) | 64 (79.0) | 20 (62.5) | 14 (82.4) | |
| Median OR time, minutes (IQR) | 338 (268–413) | 332 (268–412) | 360 (282–403) | 370 (321–423) | 0.59 |
| Median EBL, cc (IQR) | 850 (500–1350) | 800 (550–1350) | 750 (400–1350) | 950 (600–1100) | 0.82 |
| Intraoperative blood transfusion, no. (%) | 65 (50.0) | 37 (45.7) | 18 (56.3) | 10 (58.8) | |
| Time until flatus, days (IQR) | 4 (3–5) | 4 (3–5) | 4 (4–5) | 5 (4–6) | 0.007 |
| Time until bowel movement, days (IQR) | 5 (5–6) | 5 (4–6) | 6 (5–7) | 7 (6–8) | < 0.01 |
| Postoperative paralytic ileus, no. (%) | 15 (11.5) | 4 (4.9) | 3 (9.4) | 8 (47.1) | < 0.01 |
| Total parenteral nutrition, no. (%) | 14 (10.8) | 3 (3.7) | 1 (3.1) | 10 (58.8) | < 0.01 |
| Length of stay, days (IQR) | 7 (6–10) | 6 (5–8) | 8 (7–10) | 13 (8–21) | < 0.01 |
| Postoperative complications (30-day), no. (%) | | | | | < 0.01 |
| None | 54 (41.5) | 40 (49.4) | 11 (34.4) | 3 (17.6) | |
| I–II | 46 (35.4) | 32 (39.5) | 10 (31.3) | 4 (23.5) | |
| III–IV | 27 (20.8) | 9 (11.1) | 8 (25.0) | 10 (58.8) | |
| V | 3 (2.3) | 0 (0.0) | 3 (9.4) | 0 (0.0) | |

**Table 3. Identified absolute or relative contraindications to alvimopan.**

| | Total (n = 32) |
|---|---|
| Prior opioid use > 7 days | 18 (56.3) |
| Prior cardiac condition | 12 (37.5) |
| CAD s/p PCI | 4 (12.5) |
| CAD s/p CABG | 5 (15.6) |
| Arrythmia | 1 (3.1) |
| Valvular disease | 2 (6.3) |
| End-stage renal disease | 1 (3.1) |
| End-stage liver disease | – |
| Partial small bowel obstruction | – |
| Prior pancreatic or gastric anastomosis | 1 (3.1) |
| Allergy | – |

Alvimopan use in the RC population may be further increased with its incorporation into an ERAS or fast-track pathway. This set of perioperative care techniques has been developed to reduce postoperative complications and shorten LOS after RC and urinary diversion. It includes preoperative medical optimization and nutritional support, preoperative carbohydrate loading, avoidance of oral mechanical bowel preparation, use of thoracic epidural analgesia, antimicrobial and thrombosis prophylaxis, avoidance of postoperative NG tube intubation, strict perioperative fluid management, and early feeding and/or gum chewing [13]. Pruthi et al. was able to successfully implement a fast track program including several of these components in 100 consecutive patients undergoing RC with mean time to flatus of 2.2 days, mean time to BM of 2.9 days, and mean LOS of 5.0 days [14]. Metoclopramide was typically used as a prokinetic agent to promote the quicker recovery of bowel motility in earlier pathways since alvimopan was not available at the time. The inclusion of alvimopan, however, seems warranted in the evaluation of any future ERAS or fast-track protocol in the RC population although its impact on short-term outcomes as part of a larger perioperative care program is largely unknown.

**Table 4. Predictors of any 30-day complication.**

| | Multivariable | | | |
|---|---|---|---|---|
| | Odds Ratio | 95% CI | | P-value |
| | | Lower | Upper | |
| ECOG > 1 (reference: ECOG = 0) | 1.24 | 0.55 | 2.80 | 0.61 |
| Age-adjusted CCI ≥ 7 (reference: CCI ≥ 6) | 0.84 | 0.39 | 1.82 | 0.67 |
| Median pre-op creatinine, mg/dL | 2.05 | 0.65 | 6.51 | 0.22 |
| Robotic RC (reference: open) | 1.24 | 0.40 | 3.80 | 0.71 |
| Alvimopan (reference: none) | 0.35 | 0.15 | 0.82 | 0.015 |
| pT stage | | | | |
| T2 (reference: T0–T1) | 0.46 | 0.15 | 1.37 | 0.16 |
| T3–T4 (reference: T0–T1) | 0.60 | 0.26 | 1.35 | 0.22 |

**Table 5. Predictors of high-grade 30-day complications.**

| | Multivariable | | | |
|---|---|---|---|---|
| | Odds Ratio | 95% CI | | P-value |
| | | Lower | Upper | |
| ECOG ≥ 1 (reference: ECOG = 0) | 0.88 | 0.32 | 2.40 | 0.80 |
| Age-adjusted CCI ≥ 7 (reference: CCI ≥ 6) | 0.71 | 0.28 | 1.79 | 0.47 |
| Median pre-op creatinine, mg/dL | 2.72 | 0.68 | 10.92 | 0.16 |
| Robotic RC (reference: open) | 0.79 | 0.17 | 3.65 | 0.77 |
| Alvimopan (reference: none) | 0.12 | 0.044 | 0.34 | < 0.01 |
| pT stage | | | | |
| T2 (reference: T0–T1) | 1.28 | 0.35 | 4.77 | 0.71 |
| T3–T4 (reference: T0–T1) | 0.82 | 0.29 | 2.35 | 0.71 |

There are several limitations to this study in addition to its small sample size and retrospective nature. Although alvimopan was associated with better short-term postoperative outcomes, there was a selection bias toward sicker patients with more comorbidities and CV disease in the non-alvimopan group. Alvimopan use, however, was still an independent predictor of reduced complications and shorter hospitalization even after accounting for these potential counfounders on multivariate analysis, thus indicating a possible association.

Standardized ERAS pathways were also not utilized in this study, so the additional benefit of alvimopan in this setting is still not known. Additionally, since our institution is a tertiary referral center, patients often get readmitted locally and readmission rates were not available for analysis. Although we made every effort to capture postoperative 30-day complications via retrospective chart review in our electronic health record, there is a possibility of under-reporting especially if patients presented or were readmitted at outside institutions that were not captured appropriately in our system.

**Table 6. Predictors of prolonged hospitalization (> 10 days*).**

| | Multivariable | | | |
|---|---|---|---|---|
| | Odds Ratio | 95% CI | | P-value |
| | | Lower | Upper | |
| ECOG ≥ 1 (reference: ECOG = 0) | 1.05 | 0.40 | 2.75 | 0.92 |
| Age-adjusted CCI ≥ 7 (reference: CCI ≥ 6) | 1.44 | 0.58 | 3.55 | 0.43 |
| Median pre-op creatinine, mg/dL | 1.16 | 0.28 | 4.83 | 0.84 |
| Robotic RC (reference: open) | 3.05 | 0.36 | 25.66 | 0.30 |
| Alvimopan (reference: none) | 0.28 | 0.11 | 0.72 | 0.008 |
| pT stage | | | | |
| T2 (reference: T0–T1) | 0.76 | 0.19 | 3.00 | 0.70 |
| T3–T4 (reference: T0–T1) | 1.01 | 0.37 | 2.76 | 0.99 |

*Represents the highest quartile in the study population.

Epidural analgesia was also utilized in 5 patients (3.8%), which may negate the effects of alvimopan by precluding the use of opioids in the postoperative setting. Additionally, reasons for alvimopan non-usage were not documented prospectively but rather determined retrospectively based on the patient's PMH and clinical status before surgery, which creates subjectivity in the findings. Finally, this study also only reflects the utilization patterns at a single institution and may be influenced by surgeon bias as well. We were not able to stratify data based on the surgeon since no meaningful findings could be drawn due to our small sample size.

## CONCLUSIONS

Despite the known benefits of perioperative alvimopan in patients undergoing RC and urinary diversion for BC, it was under-utilized at a high-volume cancer center especially in patients with underlying CV disease or poor performance status. We recommend its inclusion into standardized perioperative care pathways to optimize its use and enhance patient recovery.

## References


1. Witjes JA, Compérat E, Cowan NC, De Santis M, Gakis G, et al. (2013) EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. Eur Urol 65: 778-792. doi: 10.1016/j.eururo.2013.11.046. PMID: 24373477
2. Ramirez JA, McIntosh AG, Strehlow R, Lawrence VA, Parekh DJ, et al. (2012) Definition, incidence, risk factors, and prevention of paralytic ileus following radical cystectomy: a systematic review. Eur Urol 64: 588-597. doi: 10.1016/j.eururo.2012.11.051. PMID: 23245816
3. Chang SS, Baumgartner RG, Wells N, Cookson MS, Smith Jr JA (2002) Causes of increased hospital stay after radical cystectomy in a clinical pathway setting. J Urol 167: 208-211. PMID: 11743307

4. Chang SS, Cookson MS, Baumgartner RG, Wells N, Smith Jr JA (2002) Analysis of early complications after radical cystectomy: results of a collaborative care pathway. J Urol 167: 2012-2016. PMID: 11956429
5. Taguchi A, Sharma N, Saleem RM, Sessler DI, Carpenter RL, et al. (2001) Selective postoperative inhibition of gastrointestinal opioid receptors. N Engl J Med 345: 935-940. doi: 10.1056/NEJMoa010564. PMID: 11575284
6. Lee CT, Chang SS, Kamat AM, Amiel G, Beard TL, et al. (2014) Alvimopan accelerates gastrointestinal recovery after radical cystectomy: a multicenter randomized placebo-controlled trial. Eur Urol 66: 265-272. doi: 10.1016/j.eururo.2014.02.036. PMID: 24630419
7. Kauf TL, Svatek RS, Amiel G, Beard TL, Chang SS, et al. (2013) Alvimopan, a peripherally acting μ-opioid receptor antagonist, is associated with reduced costs after radical cystectomy: economic analysis of a phase 4 randomized, controlled trial. J Urol 191: 1721-1727. doi: 10.1016/j.juro.2013.12.015. PMID: 24342144
8. Jansen J, Lorch D, Langan J, Lasko B, Hermanns K, et al. (2011) A randomized, placebo-controlled phase 3 trial (Study SB-767905/012) of alvimopan for opioid-induced bowel dysfunction in patients with non-cancer pain. J Pain 12: 185-193. doi: 10.1016/j.jpain.2010.06.012. PMID: 21292169
9. Webster L, Jansen JP, Peppin J, Lasko B, Irving G, et al. (2007) Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain. Pain 137: 428-440. doi: 10.1016/j.pain.2007.11.008. PMID: 18164818
10. Herzog TJ, Coleman RL, Guerrieri Jr JP, Gabriel K, Du W, et al. (2006) A double-blind, randomized, placebo-controlled phase III study of the safety of alvimopan in patients who undergo simple total abdominal hysterectomy. Am J Obstet Gynecol 195: 445-453. doi: 10.1016/j.ajog.2006.01.039. PMID: 16626607
11. Ludwig K, Enker WE, Delaney CP, Wolff BG, Du W, et al. (2008) Gastrointestinal tract recovery in patients undergoing bowel resection: results of a randomized trial of alvimopan and placebo with a standardized accelerated postoperative care pathway. Arch Surg 143: 1098-1105. doi: 10.1001/archsurg.143.11.1098. PMID: 19015469
12. Viscusi ER, Goldstein S, Witkowski T, Andonakakis A, Jan R, et al. (2005) Alvimopan, a peripherally acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery: results of a randomized, double-blind, controlled study. Surg Endosc 20: 64-70. doi: 10.1007/s00464-005-0104-y. PMID: 16333556
13. Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, et al. (2013) Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS(®)) society recommendations. Clin Nutr 32: 879-887. doi: 10.1016/j.clnu.2013.09.014. PMID: 24189391
14. Pruthi RS, Nielsen M, Smith A, Nix J, Schultz H, et al. (2009) Fast track program in patients undergoing radical cystectomy: results in 362 consecutive patients. J Am Coll Surg 210: 93-99. doi: 10.1016/j.jamcollsurg.2009.09.026. PMID: 20123338