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ORIGINAL ARTICLE

Alvimopan usage increasing following radical cystectomy

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Abstract

Purpose Alvimopan (Entereg), a peripherally acting opioid receptor antagonist, is effective in reducing the rate of postoperative ileus and length of hospital stay in patients undergoing colorectal surgery, and is now approved for use after radical cystectomy (RC). Using data from Vizient (formerly University Health System Consortium), we assessed the utilization of alvimopan and its effect on perioperative factors after RC.

Methods The Vizient database, contributed to by over 200 US academic hospitals, was evaluated from 2014 to 2016. Patients who had undergone radical cystectomy were included. Alvimopan exposure and postoperative outcomes were collected.

Results 7472 patients underwent cystectomy in the 3 years examined, with 3391 (45.4%) patients receiving alvimopan over this time period. The use of alvimopan increased from 35 to 59%. The receipt of alvimopan was associated with a decrease in perioperative morbidity (10.53% vs 19.23%, $p = 0.027$).

Conclusion This study, the largest to examine the real-world utilization of alvimopan since FDA approval for RC, shows that alvimopan utilization has increased substantially and is associated with reduced perioperative morbidity in patients undergoing cystectomy.

Keywords Cystectomy · Bladder cancer · Alvimopan · Ileus · Vizient

Abbreviations

RC	Radical cystectomy with urinary diversion
ERAS	Enhanced recovery after surgery
POI	Postoperative ileus

Introduction

Radical cystectomy (RC) and urinary diversion remain the standard treatment for muscle-invasive bladder cancer and are also recommended for high-risk non-muscle-invasive disease (AUA Clinical Guidelines). Despite advancements in the surgical techniques and introduction of minimally invasive surgeries including robotic surgery, radical cystectomy and urinary diversion continue to have high complication rates [1–3].

Many of the complications after RC stem from gastrointestinal tract manipulation due to bowel resection and reanastomosis causing postoperative ileus (POI) and opioid-induced constipation (OIC), both of which contribute to prolonged length of stay (LOS) [4, 5].

Although opioids are potent analgesics, they cause opioid-induced constipation, which is defined as "a condition in which a person has fewer than three spontaneous bowel movements in a week or has bowel movements with hard, dry, and small stools that are painful/difficult to pass" [6, 7]. This condition can be troubling for a patient who is recovering from RC and negatively effects quality of life, compliance, and physical activity [6, 7].

Postoperative ileus and opioid-induced constipation are believed to be induced by stimulation of mu receptors that are abundant throughout intestinal mucosa and ileal submucosa. Mu receptor stimulation leads to decreased peristalsis, increased gastric emptying time, decreased mucosal secretions, and increased sphincter tone. Interestingly, mu receptors do not develop tolerance towards opioids, contrary to other opioid receptors [6, 8].

Alvimopan, a peripherally acting mu receptor antagonist, was FDA approved in 2008 for reduction of postoperative ileus after partial large or small bowel resection surgery [7,

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9]. Based on the additional RCTs, it was FDA approved for use following radical cystectomy in 2013 [10]. Subsequent studies have shown enhanced recovery and reduced cost of hospital stay associated with perioperative use of alvimopan in patients undergoing radical cystectomy [10–12].

We hypothesize that since FDA approval in 2013, the alvimopan use has increased following radical cystectomy, likely as part of comprehensive ERAS protocols, and is associated with improved postoperative outcomes.

Methods

Database description

Vizient, formerly University Health System Consortium (UHC), serves an alliance of nearly 200 US academic medical centers and their affiliated hospital systems and provides administrative, clinical, and financial data at the patient level. This includes only inpatient stay information such as demographics, LOS, morbidity, risk-adjusted mortality, and costs. Vizient has no information on pathologic staging, post-discharge mortality or complications.

Data analysis

Vizient Clinical Data Base/Resource Manager was searched for any diagnosis of bladder cancer (ICD-9 and 10 codes 188–188.9, C67, C670–675, C678, C679, C791) and for procedural codes for radical cystectomy (ICD-9CM and 10 5771, 0TTB0ZZ) performed from 2014 to 2016. The receipt of alvimopan was used to stratify the groups. The rate of postoperative ileus (ICD-9 5601, ICD-10 K56), 'any complication', and mortality were calculated by the receipt of alvimopan. 'Any complication' is an internal Vizient database grouping definition that includes stroke, pneumonia, myocardial infarction, anesthesia complications, infection, shock, C. difficile, and hemorrhage. Basic demographics are also reported although tumor staging is not available. Significance for the study was set at $p < 0.05$ for one-sided *T* tests and Chi-square analyses.

Main outcome measures

The receipt of alvimopan was the primary outcome of interest, with postoperative ileus rate, perioperative complication rate, and mortality stratified by alvimopan use as secondary outcomes. Alvimopan use was followed over time to determine the changing utilization.

Results

The total number of patients undergoing cystectomy from 2014 to 2016 was 7472. Of those, 3391 received alvimopan. Table 1 details the characteristics of patients receiving alvimopan compared to those who did not receive alvimopan. The percentage of patients receiving alvimopan increased from 35.3% in 2014 to 59.8% in 2016 (Table 2). The use of alvimopan was associated with a statistically significant trend over time in the reduction of ileus ($p = 0.032$) (Table 3). The rate of any complication was decreased in patients who received alvimopan (10.53% vs 19.23%, $p = 0.027$), but mortality was not affected (0.91% vs 1.59%, $p = 0.58$) (Table 4).

Discussion

In this study, which we believe is the largest to evaluate the real-world use of alvimopan since it received FDA approval for use in patients undergoing radical cystectomy,

Table 1 Patient demographics by alvimopan use

Variable	Alvimopan % (*n*)	No alvimopan % (*n*)	*p* value
Received	45.4 (3391)	54.6 (4081)	
Age	68.3	67.4	
Sex			
Male	44.6	55.3	0.38
Female	40.4	59.6	
Race			
White	84.8	85.3	0.77
Black	5.9	5.4	
Asian	2.4	2.5	
Other	6.9	6.8	

Table 2 Patients receiving alvimopan over time

Year	Using (%)	Not using (%)
2014	35.3	64.7
2015	47.6	52.4
2016	59.8	40.2

Table 3 Ileus rate after radical cystectomy

Year	Using (%)	Not using (%)	*p* value
2014	19.02	23.54	0.288
2015	13.25	20.97	0.058
2016	9.51	19.21	**0.013**
Overall	13.95	21.90	

Bold values indicate clinically significant *p* values based on $p < 0.05$

Table 4 Perioperative outcomes between patient groups

Variable	Alvimopan % (*n*)	No alvimopan % (*n*)	*p* value
Ileus	13.95 (473)	21.90 (895)	0.054
LOS (days)	7.77	10.1	**0.003**
Mortality	0.91 (31)	1.59 (54)	0.58
Any complication	10.53 (357)	19.23 (652)	**0.027**

Bold value indicates clinically significant *p* values based on $p < 0.05$

we provide insights into the utilization of this medication by urologists at the hospital and patient level as well as the evidence of significant benefits of its usage.

Using the Vizient database, we show the trend, in the use of alvimopan by urologists after RC, is increasing. Specifically, alvimopan is more frequently given to patients following FDA approval in 2013, increasing from 35% of patients in 2014 to 60% in 2016. This trend mirrors the initial adoption by colorectal surgeons, where the use of alvimopan in colorectal patients increased from 66% to 82% from 2009 to 2013 [13].

When alvimopan was initially granted FDA approval in 2008, it was described as a drug to benefit patients undergoing ERAS protocols for open colorectal surgery given its activity as a peripherally acting opioid antagonist [14]. Despite good evidence of its efficacy, there were multiple concerns at that time regarding its safety profile and its overall cost [15, 16]. In a phase III trial published in 2005, a non-statistically significant trend towards increased cardiovascular morbidity, specifically myocardial infarction, was seen in patients who received alvimopan [16]. This limited the drug's early use. Subsequently, however, the vast majority of studies failed to confirm this finding, and most have shown a decrease in the overall morbidity and mortality with the use of alvimopan [13, 17–20]. The urologic data from this study support this finding as well.

Prior to the pivotal RCT by Lee et al. in 2013 [10], there was a paucity of studies examining its risks and benefits in urologic patients. FDA approval soon followed. Prior studies in colorectal patients were not considered as adequate evidence, given that only one reviewed alvimopan use in patients who had undergone surgery involving the small bowel, a key aspect of RC [20]. The most recent AUA 2017 guideline on muscle-invasive bladder cancer now supports its use with a strong recommendation based on grade B evidence [21]. Before this, even among urologic oncology bladder cancer experts, there was no widespread adoption of alvimopan. In a general sense, this may be due to a lack of consensus regarding ERAS programs for the patient population. A recent survey of 61 experts in urologic oncology revealed that only 39 regularly practiced ERAS protocols, and of those that did, over 50% chose only some of the commonly accepted ERAS protocols [22]. Those that did not use ERAS did so for multiple reasons, but the most common responses were "lack of convincing evidence" that various ERAS protocols were effective, and a lack of belief in these principles in general. Although this is a relatively small subset of practicing urologists, it likely reflects the reasons provided by those not adopting alvimopan into their practice. We expect that FDA approval and the AUA 2017 guidelines will both further increase the alvimopan use.

RC with urinary reconstruction using bowel poses significant morbidity and mortality to patients, with an overall complication rate of 25–60% and a mortality rate of 1–3% [1–3, 23, 24]. Therefore, any management change that reduces complications and LOS should be viewed favorably by practicing urologists. Alvimopan has been shown to reduce the rates of postoperative ileus, time to toleration of diet, time to first bowel movement, and length of stay [10, 25–28]. Our data contribute positively to the current body of research suggesting that alvimopan reduces the rates of POI and additional complications. Of particular interest is the statistically significant decrease in the rate of 'any complication'. While this is a variable group of complications within Vizient, complication reduction is a goal of all surgical management strategies. While these data do not prove a direct effect of alvimopan on this rate, there is likely a contributory effect. This is more likely an effect of greater adoption of ERAS protocols in general, though we could not determine the protocols from this dataset.

There are several limitations to this study. This study is retrospective in nature and thus, has selection bias inherent to its design but captures real-world usage. In comparing the rate of POI in patients who received or did not receive alvimopan, patient-related variables including age, body mass index (BMI), or comorbidities have not been taken into account, because the publicly available dataset gives aggregate patient-level data only. No staging data are available. Surgeon- and procedure-related variables (case volume, laparoscopic or open surgery, surgical time, etc.) were also not included, as these were mostly unavailable. Furthermore, the definition of postoperative ileus was obtained from CPT coding alone and therefore, was not standardized throughout the hospitals. Ileus diagnoses may not have been included or miscoded in the initial hospitalization, resulting in undercounting. A number of factors that affect POI were also not recorded in this data, including bowel handling during surgery, surgeon caseload and expertise, perioperative fluid resuscitation, and concurrent use of opioid medications. Lastly, the Vizient database documented alvimopan use if the patients received at least one dose of alvimopan. It was not possible to determine if all the patients in the alvimopan group received all 15 doses of the medication as suggested by the manufacturer.

Conclusions

In this study, utilizing data from Vizient, we have shown that usage of alvimopan is increasing for patients undergoing radical cystectomy. Additionally, our data also support the previously published studies detailing a likely decrease in postoperative ileus and a significant decrease in the overall morbidity from RC. Given the high rate of postoperative complications from this surgery, alvimopan can clearly play an important role in the postoperative management of these patients, especially as part of an ERAS protocol. These findings suggest that use of alvimopan will likely continue to rise in the United States, and that it is of significant benefit to the patients.

Author contributions JB data analysis, manuscript writing/editing. AP manuscript writing/editing. DO protocol/project development, data collection. CD protocol/project development, data collection and management, manuscript writing/editing

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Statement of human rights For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual parties included in the study.

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