



Alvimopan for post-radical cystectomy ileus: what should we know?

Catriona Duncan^{1,2#}, Jiasian Teh^{1,3,4#}, Nathan Lawrentschuk^{1,3,4}

¹Department of Surgery, Urology Unit, University of Melbourne, Austin Hospital, Melbourne, Australia; ²North Eastern Urology, Melbourne, Australia; ³Department of Surgical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; ⁴EJ Whitten Prostate Cancer Research Centre at Epworth Healthcare, Melbourne, Australia

#These authors contributed equally to this work.

Correspondence to: Nathan Lawrentschuk. Department of Surgery and Olivia Newton-John Cancer Research Institute, University of Melbourne, Melbourne, Australia; Department of Surgical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia. Email: lawrentschuk@gmail.com.

Provenance: This is an invited Editorial commissioned by Section Editor Xiao Li (Department of Urology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China).

Comment on: Belle JD, Pooli A, Oleynikov D, *et al.* Alvimopan usage increasing following radical cystectomy. *World J Urol* 2018. [Epub ahead of print].

Submitted Dec 21, 2018. Accepted for publication Jan 04, 2019.

doi: 10.21037/tau.2019.02.01

View this article at: <http://dx.doi.org/10.21037/tau.2019.02.01>

Post-operative ileus is a significant issue encountered by numerous patients following radical cystectomy and urinary diversion. It can contribute to prolonged length of hospital stay, increased post-operative morbidity and significant patient discomfort (1). The causes of POI are multifactorial and include manipulation of the gastrointestinal tract due to bowel resection and re-anastomosis, inflammatory mediators, electrolyte imbalances, and use of systemic opioids. Traditional opioids, which bind to mu receptors in the gut, currently play a key role in post-operative pain management after radical cystectomy and can contribute to the development of POI. Prophylactic measures to prevent POI such as the use of prokinetic agents like metoclopramide, use of regional anaesthesia and aggressive and early ambulation post operatively are practiced routinely to expedite gut functioning (2,3).

What is alvimopan?

Alvimopan (Entereg, Cubist Pharmaceuticals) is an U.S. Food and Drug Administration (FDA) approved mu opioid receptor antagonist which acts peripherally. When it is started pre-operatively, it has been demonstrated to hasten intestinal motility and reduce the duration of post-operative ileus. Unlike non-selective opioid antagonists such as naloxone, which reverse constipation, alvimopan does not reverse the analgesia provided by systemic opioids as it does

not cross the blood-brain barrier. It was approved by the US-FDA (4) for use following colorectal surgery in 2008 and following radical cystectomy in 2013 (5) following a randomised controlled trial (RCT) (6) which demonstrated reduced time to gastrointestinal recovery when compared to placebo, measured as a composite score determined by a tolerance of solid oral intake and first bowel movement. In addition, there was no statistically significant difference in the cardiovascular event of interest rate between the two groups (8.4% *vs.* 15.3%, $P=0.09$). There were 5 (3.5%) deaths in the alvimopan group compared with 4 (2.9%) in the placebo group but these were considered unrelated to alvimopan administration. This was of particular interest as previous studies investigating alvimopan use over 21 months for in patients with chronic opioid requirements demonstrated increased reports of myocardial infarction in the alvimopan group, the majority of which occurred in the 1–4 months window (4).

Initially, the perceived cost and logistics involved in storing and dispensing alvimopan prohibits its use on a regular basis. Kauf *et al.* (7) undertook a probabilistic economic analysis to evaluate the costs associated with the use of alvimopan following radical cystectomy within the randomised clinical trial. They concluded that alvimopan reduced the cost of hospitalisation through the reduction in length of stay and decreased the use of health care services relating to the management of post-operative ileus. Further

cost effectiveness modelling by Hilton *et al.* (8) states based on the average cost of alvimopan of \$700 per patient, use of alvimopan can result in a cost benefit if it causes a risk reduction of POI of 44%, with an overall likelihood that use of alvimopan will result in cost savings in 74.2% of patients undergoing radical cystectomy. Presently, the cost of alvimopan still presents a barrier to its regular use. The cost of 15 doses of alvimopan is approximately 250 times the cost of metoclopramide when used as a dose of 10 mg four times a day intravenously.

The cost effectiveness was also considered in a retrospective review by Manger *et al.* (9), which demonstrated that the reduction in mean length of stay by 1.9 days which was associated with a reduction in cost of stay of 20% (\$USD 40,604 *vs.* \$USD 32,442).

A retrospective review by Belle *et al.* (5) aimed to assess the rate of alvimopan use following radical cystectomy after its approval for this indication by the FDA in 2013. This review demonstrated a trend of increasing utilisation over time, with a baseline of 35.3% of patients receiving alvimopan in 2014, increasing to 59.8% if patients receiving alvimopan after radical cystectomy in 2016 across more than 200 academic hospitals in the USA included in this study. Consistent with other studies, Belle *et al.* confirmed a reduction in length of stay in patients receiving alvimopan with a reduction in the rates of any complications. In addition, mortality rates were not affected.

Currently in the USA, the approved use of alvimopan is in the immediate post-operative setting following partial bowel resection with a primary anastomosis, with a dosing schedule of 12 mg 30 minutes to 5 hours pre-operatively, with post-operative twice daily dosing until discharge or day 7 post-procedure, to a maximum of 15 doses. At this time, alvimopan is only available through the Entereg Access Support and Education (E.A.S.E.) program to restrict its use to hospitals, due to the risk of myocardial infarction with prolonged use (10). The use of alvimopan elsewhere is limited by access.

Studies showing efficacy of alvimopan

Delaney *et al.* performed a pooled analysis of 3 randomised, double-blind, placebo-controlled, phase III, parallel-group, multicentre trials which investigated the safety and efficacy of alvimopan after bowel resection operations. They found significantly accelerated GI recovery in patients who received alvimopan compared to the placebo group (11).

Traut *et al.* analysed 39 RCTs, which included 15

prokinetic agents of different drug classes and 10 studies that involved comparisons of prokinetic agents. Commonly used drugs such as cholecystokinin-like drugs, erythromycin, vasopressin, propranolol had insufficient evidence to demonstrate benefit. However, 6 RCTs supported the use of alvimopan. This was published in the Cochrane database systematic review in 2008 (12).

Studies specifically looking at use following radical cystectomy include a systematic review and meta-analysis by Cui *et al.* (13), which included 1 randomised trial and 4 case control studies, including a total of 613 patients, who underwent radical cystectomy of whom 294 (49%) were administered alvimopan. Meta-analysis revealed reduced time to toleration of liquid and solid foods, first bowel movement and length of stay in patients who had received alvimopan. As bladder cancer is common yet in many ways still an overlooked urological malignancy, improvements in outcomes have lagged behind other urological cancers such as prostate cancer (14). Further investigation into alvimopan use specifically following radical cystectomy for bladder cancer has the potential to improve outcomes in this patient group.

Furthermore, alvimopan is not as effective if it is used once ileus has developed, the FDA recommends commencing therapy in the preoperative setting. Other supportive measures such as optimisation of electrolytes, mobilisation, ambulation, early enteral feeds and laxatives should be continued.

Conclusions

Alvimopan can be used in the management of eligible patients following radical cystectomy in the USA through the access scheme. Alvimopan is increasingly being used to reduce morbidity, length of hospitalisation and costs associated with radical cystectomy. However, the expensive nature of the drug and the logistics involved in obtaining alvimopan for use currently prohibit clinicians from using it on a regular basis in the peri-operative setting. Early retrospective analysis has demonstrated that these effects are mirrored in the real-world use of alvimopan following radical cystectomy, however, larger prospective trials are needed to establish whether these effects hold up under more vigorous scrutiny.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Sathianathan NJ, Kalapara A, Frydenberg M, et al. Robotic-assisted radical cystectomy vs open radical cystectomy: systematic review and meta-analysis. *J Urol* 2019. [Epub ahead of print].
2. Saclarides TJ. Current Choices—Good or Bad—for the Proactive Management of Postoperative Ileus: A Surgeon's View. *Journal of PeriAnesthesia Nursing* 2006;21:S7-15.
3. Udovich C, Perera M, Huq M, et al. Hospital volume and perioperative outcomes for radical cystectomy: a population study. *BJU International* 2017;119:26-32.
4. Administration, U.S.F.A.D., FDA Approved Drug Products: Entereg. 2008, U.S. Food and Drug Administration: Silver Spring, Maryland.
5. Belle JD, Pooli A, Oleynikov D, et al. Alvimopan usage increasing following radical cystectomy. *World J Urol* 2018. [Epub ahead of print].
6. Lee CT, Chang SS, Kamat AM, et al. Alvimopan accelerates gastrointestinal recovery after radical cystectomy: a multicenter randomized placebo-controlled trial. *Eur Urol* 2014;66:265-72.
7. Kauf TL, Svatek RS, Amiel G, et al. 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* 2014;191:1721-7.
8. Hilton WM, Lotan Y, Parekh DJ, et al. Alvimopan for prevention of postoperative paralytic ileus in radical cystectomy patients: a cost-effectiveness analysis. *BJU Int* 2013;111:1054-60.
9. Manger JP, Nelson M, Blanchard S, et al. Alvimopan: A cost-effective tool to decrease cystectomy length of stay. *Cent European J Urol* 2014;67:335-41.
10. Merck. Entereg (Alvimopan). Merck & Co. 2018. Available online: <https://www.merckconnect.com/entereg/dosing-administration/>. Accessed 12/20/18 2018.
11. Delaney CP, Wolff BG, Viscusi ER, et al. Alvimopan, for postoperative ileus following bowel resection: a pooled analysis of phase III studies. *Ann Surg* 2007;245:355-63.
12. Traut U, Brügger L, Kunz R, et al. Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults. *Cochrane Database Syst Rev* 2008;(1):CD004930.
13. Cui Y, Chen H, Qi L, et al. Effect of alvimopan on accelerates gastrointestinal recovery after radical cystectomy: A systematic review and meta-analysis. *Int J Surg* 2016;25:1-6.
14. Lawrentschuk N. Bladder cancer- time for a higher profile in our region. *BJU Int* 2017;119:5.

Cite this article as: Duncan C, Teh J, Lawrentschuk N. Alvimopan for post-radical cystectomy ileus: what should we know? *Transl Androl Urol* 2019;8(Suppl 1):S96-S98. doi: 10.21037/tau.2019.02.01