Alvimopan: How Much are You Willing to Pay for Results?

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Pharmacy Grand Rounds
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To use or not to use?

• How efficacious is alvimopan for post-operative ileus?
• Is the cost of alvimopan worth the benefit?
• Is alvimopan over-utilized for inappropriate indications?
• Cost:
  • $62.50 per capsule when approved in 2008
  • $158 per capsule (2017)
Objectives

• Outline the incidence, severity, and resulting economic burden of postoperative ileus (POI)
• Identify the risks and benefits of treatment options for POI
• Discuss intended versus actual use of alvimopan and the impact it has on cost of care.
Post-operative ileus (POI)

- Ileus: absence of intestinal peristalsis after ruling out mechanical obstruction
- POI: ileus that occurs after surgery
- Common complication of surgery
- 22 million surgeries annually → 10% experience POI

Symptoms of POI

- Delayed / absent flatus, stool, or bowel sounds > 3 days after surgery
- Gastrointestinal material accumulation with associated nausea / vomiting
- Inability to tolerate / advance diet
- Abdominal pain / distension

Factors associated with POI

- Local manipulation & trauma
- Inflammatory responses
- Opioid use
- Electrolyte & water imbalance

Incidence of POI in surgery

- Laparotomy (40%)
  - Bowel resection
    - Small bowel resection (19.2%)
    - Large bowel resection (14.9%)
  - Cystectomy (17 - 23%)
  - Total abdominal hysterectomy (3%)
- Hip/knee arthroplasty (4%)

Assessment Question #1

Which of the following is true of POI?

A. POI is solely due to opioid use
B. POI only occurs with intra-abdominal surgeries
C. POI occurs in 1-2% of surgical procedures
D. POI is diagnosed as delayed return of bowel function for more than 3 days
Burden of POI

• Most common cause of delayed hospital discharge following abdominal surgery (mean 2-3 days)
• Increased postoperative morbidity / complications
  • Pneumonia / atelectasis
  • Poor wound healing
  • Patient discomfort / symptoms
• Readmissions
  • Average 10% readmitted (3% due to ileus or bowel obstruction)

Economic burden of POI

- Goldstein et al (2007)
  - Endpoint: Cost per hospitalization - difference between patients with or without diagnosed POI
  - Procedures: Open laparotomies; laparoscopic, orthopedic, thoracic surgeries (1.6 million total)
  - Incidence: 8.5% of patients diagnosed with POI
  - Annual cost attributed to POI $1.46 billion

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>With POI</th>
<th>Without POI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay</td>
<td>11.5 days</td>
<td>5.5 days</td>
</tr>
<tr>
<td>Cost</td>
<td>$18,877</td>
<td>$9,460</td>
</tr>
</tbody>
</table>
Interventions to minimize and reduce POI

Pain control
- Minimize systemic opioids
- Epidural anesthesia
- NSAIDs, gabapentin

Early Ambulation

Metabolic Support
- Electrolyte replacement
- Restriction of perioperative fluids

GI stimulation
- Early enteral feedings
- Medications (prokinetics)
- Sham feeding (gum chewing)

Pharmacologic management of POI

- 2008 Cochrane systematic review of 39 randomized controlled trials
- 4,615 patients
- Underwent major abdominal surgery
- Evaluated 15 systemic acting prokinetic agents
- Failure to show benefit in management of POI

Assessment Question #2

Which of the following is true about treatment for POI?

A. Prokinetics have shown a consistent benefit in POI
B. Gum chewing may have benefit with reducing POI
C. Early oral intake increases risk of POI
D. Route of opioids for pain control does not affect POI
Peripheral acting mu-opioid receptor antagonists

Alvimopan (Entereg) [approved May 2008]
- Indication: To accelerate the time to upper and lower GI recovery following surgeries including partial bowel resection with primary anastomosis

Methylnaltrexone (Relistor) [approved April 2008]
- Indication: Opioid-induced bowel dysfunction in chronic pain or palliative care after failing laxative therapy
- Mixed / uncertain efficacy with POI
Alvimopan Mechanism of Action

Pain and Narcotic Analgesics

Alvimopan (ADL 8-2698) Mechanism of Action

Narcotic Analgesics:
- morphine
- codeine
- hydrocodone
- oxycodone
- fentanyl

Central Opioid Receptors

Narcotic Side Effects:
- Sedation
- Respiratory Depression
- Addiction

Peripheral Opioid Antagonist

Peripheral Opioid Receptors

Alvimopan (ADL 8-2698) Selectively Antagonizes GI Opioid Receptors; No Effect on CNS Opioid Receptors

Opioid Bowel Dysfunction

Alvimopan pharmacokinetics

- Poor bioavailability (~6%)
- Converted to active metabolite by gut flora
- Absorption: Peak plasma concentration → ~ 2 hours post-dose
- T½ = 10 – 18 hours
- Elimination: 35% renal, 65% biliary
  - No renal / hepatic adjustments necessary

Entereg® (alvimopan) package insert. 2017
Alvimopan

- 12 mg oral capsule

Dosing:
- Take 30 minutes to 5 hours BEFORE surgery
- 12 mg twice daily beginning the day AFTER surgery until discharge

- Maximum of 7 days or 15 doses
- Common adverse effects: dyspepsia (≥ 1.5%)
- Contraindications:
  - In patients who have used opioids for more than 7 consecutive days before its use

Entereg® (alvimopan) package insert. 2017
## Cardiovascular events

**Study GSK014 (opioid-induced constipation)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 267)</th>
<th>Alvimopan 0.5 mg twice daily (n = 538)</th>
<th>Relative risk (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>7 (1.3)</td>
<td>7.46</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0</td>
<td>3 (0.56)</td>
<td>3.48</td>
</tr>
<tr>
<td>Cerebrovascular event (non-fatal)</td>
<td>0</td>
<td>1 (0.19)</td>
<td>1.49</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
<td>1 (0.19)</td>
<td>1.49</td>
</tr>
<tr>
<td>Serious arrhythmia</td>
<td>0</td>
<td>2 (0.37)</td>
<td>2.49</td>
</tr>
<tr>
<td>Death from cardiovascular event</td>
<td>0</td>
<td>1 (0.19)</td>
<td>1.49</td>
</tr>
<tr>
<td>All-cause death</td>
<td>2 (0.75)</td>
<td>2 (0.37)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

All RR non-statistically significant.

Mortensen E. OBD study GSK014. 2008
Warnings and Precautions

- **Black Box warning:**
  - Potential risk of MI with long-term use: For short-term hospital use only

- **Available only through ENTEREG Access Support and Education (E.A.S.E) Risk Evaluation and Mitigation Strategy (REMS) Program**
  - Providers have educational materials on limiting alvimopan to short-term, inpatient use
  - Limit of 15 doses per patient
  - Will not be dispensed upon discharge

Standardized accelerated post-operative care pathway

- NGT removal after surgery or by noon on post-op day 1 (POD #1)
- Early Ambulation (POD #1)
- Liquid diet (POD #1)
- Solid diet (POD #2)

Efficacy endpoints – Phase III trials

- **GI2**
  - Toleration of solid food and first bowel movement

- **GI3**
  - Toleration of solid food and either first flatus or bowel movement

- **Other outcomes**
  - Length of stay (LOS), time that discharge orders were written (DOW), postoperative nasogastric tube (NGT) insertion

References:
North American Phase III trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Doses</th>
<th>Pts</th>
<th>Indications</th>
<th>Endpoints</th>
<th>Significant</th>
</tr>
</thead>
</table>
| Viscusi et al (2005) | Placebo 6 mg 12 mg | ~ 220 per group | Bowel resection (n = 437)  
Hysterectomy (n = 200) | GI-2  
GI-3  
DOW | GI-2: 6 mg, 12 mg  
GI-3: 12 mg  
DOW: 6 mg, 12 mg |
| Delaney et al (2005) | Placebo 6 mg 12 mg | ~ 150 per group | Bowel resection (n = 303)  
Hysterectomy (n = 129) | GI-2  
GI-3  
DOW | GI-2: 6 mg  
GI-3: 6 mg  
DOW: 6 mg |
| Wolff et al (2004)   | Placebo 6 mg 12 mg | ~ 150 per group | Bowel resection (n = 451)  
Hysterectomy (n = 18) | GI-2  
GI-3  
DOW | GI-2: 6 mg, 12 mg  
GI-3: 6 mg, 12 mg  
DOW: 6 mg,12 mg |
Delaney et al (2007): Pooled meta-analysis

- Included only BR cohorts from the prior three Phase III trials

<table>
<thead>
<tr>
<th>Mean time to recovery of GI function endpoints</th>
<th>Placebo</th>
<th>Alvimopan 6 mg</th>
<th>Alvimopan 12 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>341</td>
<td>356</td>
<td>361</td>
</tr>
<tr>
<td>GI-3</td>
<td>118.8 hrs</td>
<td>-12.4 hrs</td>
<td>-14.8 hrs</td>
</tr>
<tr>
<td>GI-2</td>
<td>128.1</td>
<td>-15 hrs</td>
<td>-18.3 hrs</td>
</tr>
<tr>
<td>DOW</td>
<td>146.8</td>
<td>-16 hrs</td>
<td>-18.4 hrs</td>
</tr>
</tbody>
</table>

Conclusion: Alvimopan accelerated GI recovery and reduced post-operative morbidity and readmission


**Objective**
- Investigate the safety and efficacy of alvimopan in pts who undergo simple total abdominal hysterectomy

**Study design**
- 519 women randomized to receive alvimopan 12 mg (n=413) or placebo (n=106) ≥ 2 hrs before operation, then 2x/day x 7 days. Efficacy assessed for 7 postop days.

**Results**
- No difference between alvimopan and placebo in GI-3 (-1.9 hrs), toleration of first solid food (-1.6 hrs), or DOW (-2.3 hrs). Statistically significant reduction in GI-2 (-20.2 hrs), primarily driven by time to first BM (-22.2 hrs).

**Conclusion**
- Results did not provide enough evidence to warrant alvimopan use outside the setting of BR surgeries.

Ludwig K et al (2008)

- Multi-center, randomized, placebo-controlled, double-blind study

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Dose*</th>
<th>Patients</th>
<th>Indications</th>
<th>Endpoints</th>
<th>Significant</th>
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</thead>
<tbody>
<tr>
<td>Ludwig et al</td>
<td>2008</td>
<td>Placebo</td>
<td>312</td>
<td>Bowel resection</td>
<td>GI-2</td>
<td>GI-2: -20 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 mg</td>
<td>317</td>
<td></td>
<td>GI-3</td>
<td>GI-3: -16 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DOW</td>
<td>DOW: -17 hrs</td>
</tr>
</tbody>
</table>

*Dose given 30-90 minutes before surgery

- Conclusion
  - Alvimopan maintained efficacy when doses close to time of surgery
  - FDA-approved labeling includes dosing 30 minutes before surgery

Bell et al (2009)

- Purpose: analyze economic effect of alvimopan use in 4 randomized, double-blind, placebo-controlled, Phase III, North American trials

- Costs
  - $62.50 per 12 mg capsule (WAC – 2008)
  - Inpatient LOS: $1,600 daily
    - Comparative cost database (bowel resections from 500+ US hospitals)
    - U.S. Census Bureau: Average cost per day for inpatient stay in general, regardless of procedure
Bell et al (2009)

• Results
  • Mean cost of 8.9 doses was $558
  • Mean hospital LOS \(\rightarrow\) 1 full day less than placebo (savings of $1600 per day)
  • 44% relative reduction in prolonged LOS (defined as DOW greater than 7 post-op days)

• Conclusion
  • Mean estimated hospital cost: $879 - $977 less for patients who received alvimopan compared with placebo

Touchette et al (2012)

Objective

• To determine whether alvimopan use in pts undergoing BR by laparotomy is associated with lower total costs compared with standard care.

Data sources

• 4 Phase III trials, 2 pooled analyses, 1 meta-analysis

Main results

• Costs for alvimopan were $570 based on average of 9.5 doses. Mean reduction in DOW was 18.4 hrs. Alvimopan reduced hospitalization costs by $2021.

Conclusion

• Alvimopan was cost saving for prevention of POI in pts undergoing BR by laparotomy. This finding is not applicable to less-invasive laparoscopic surgeries.

Keller et al (2016)

Objective
- Evaluate the benefit of alvimopan in laparoscopic colorectal surgery with an enhanced recovery pathway (ERP)

Methods
- Laparoscopic colorectal cases stratified into alvimopan and control cohorts. Main outcomes were LOS, complications, readmissions, and costs in alvimopan and control groups.

Results
- 321 patients analyzed in each cohort. LOS (3.69 vs 3.49 days; p=0.16) readmission (2.8% vs 3.7%; p=0.66), reoperation rates (2.2% vs 1.6%; p=0.77) comparable for alvimopan and controls, respectively.

Conclusions
- Alvimopan added no clinical benefit in patient outcomes in laparoscopic colorectal surgery with an ERP. The control group had a cost savings of $27,577 compared with alvimopan group.

Assessment Question #3

Which of the following is correct about the use of alvimopan for post-operative ileus (POI)?

A. Alvimopan may be used outpatient with zero refills ordered.
B. Alvimopan has not demonstrated consistent efficacy in laparoscopic procedures.
C. Alvimopan can be used for chronic opioid-induced constipation.
D. Alvimopan use is associated with significant CNS withdrawal in chronic opioid users.
Mayo Clinic Health System – Franciscan Healthcare (La Crosse, WI)

- Mini-DUE conducted
  - 1/1/17 – 3/31/17
  - 6 patients (29 doses)

- Indications:
  - 3 laparotomy cases
    - Two partial large bowel resections
    - One partial small bowel resection
  - 3 laparoscopic cases
    - Two partial large bowel resections
    - One multi-site GI procedure
Mayo Clinic Health System – Franciscan Healthcare (La Crosse, WI)

- Current cost: $158 per 12 mg capsule (AWP)
- Recent use
  - 2016: 187 doses given (~ $29,000)
  - 2017: 29 doses given (3 months of data)
- Economic implications
  - Cost of 29 doses → $4,582
  - Appropriate use (3 patients) → If 3 patients were discharged a day earlier → savings of $4,800
  - Uncertain/no benefit (3 patients) → if half of the doses (n=15) were inadvertently given, potential cost savings of $2,370
Future steps

• Evaluate whether our site is optimizing use of an enhanced recovery pathway

• Future residency project:
  • Retrospective review of indications for use
  • Prospective study of alvimopan use in all surgical patients

• As health care costs continue to increase, reductions in unnecessary costs are important to hospital efficiency and patient care
Conclusions

• POI contributes to significant morbidity and remains a costly surgical complication.

• Alvimopan is the only FDA-approved option to reduce the duration of POI, with use limited to the setting of BR surgery.

• Health systems should ensure that enhanced surgical pathways are in place to optimize outcomes for surgical pts
  • Minimally invasive surgery, early ambulation, early feedings, prompt removal of NG tubes, and minimization of systemic opioids

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Uncertain / No benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Laparotomy</td>
<td>- Laparoscopic</td>
</tr>
<tr>
<td>- Bowel resection with anastomosis</td>
<td>- Hysterectomy</td>
</tr>
<tr>
<td>- Radical cystectomy</td>
<td>- Opioid-induced constipation with chronic use</td>
</tr>
<tr>
<td>- Bowel resection with ostomy placement</td>
<td></td>
</tr>
</tbody>
</table>
Questions?
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