A systemic review and meta-analysis of Aprepitant Combination Regimens (ACR) for prevention of Chemotherapy induced Nausea and Vomiting (CINV) in adults

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• Nausea and vomiting are devastating side-effects of treatment with antineoplastic agents.
• CINV can lead to conditioning after repeated cycles of therapy.
• Metabolic imbalances.
• Degeneration of self care and functional ability.
• Anorexia
• Mental status, wound dehiscence and esophageal tears.
Management

- Dopamine receptor blockers, serotonin receptor antagonists and steroids help.
- Unfortunately the effectiveness of these drugs remained largely limited to acute emesis even when started before the first dose of the anticancer drug at each cycle of treatment.
- The role of currently available drugs in the management of delayed emesis (occurring after 24 h) is very less.
• Drugs which block substance P from binding to neurokinin type 1 (NK₁) receptors can be used as antiemetic agents as these neurotransmitters are implicated in the pathophysiology of emesis.
• Aprepitant is the first member of this new class of antiemetic drugs.
CINV treatment and prophylaxis

5-HT3 antagonists
- Dolasetron
- Granisetron
- Ondansetron
- Palonosetron

NK1- blocker
- Aprepitant

Corticosteroids
- Methylprednisolone
- Dexamethasone

Antipsychotics
- Prochlorperazine
- Olanzapine

Dopamine antagonists
- Metoclopramide

Cannabinoids
- Nabilone
- Dronabinol

Introduction

• Various randomized controlled trials (RCTs) have shown improved outcomes with addition of Aprepitant to standard antiemetic treatment (SAT) for preventing CINV in adults.

• We conducted a systematic review and meta-analysis to study the overall impact of Aprepitant in CINV prevention.
Methods

• Search to retrieve articles was conducted in Pubmed and Ovid databases, and American Society of Clinical Oncology meetings proceedings.
• Nausea, vomiting, chemotherapy, aprepitant.
• Search included RCTs that studied aprepitant combination with SAT for prevention of CINV in adult cancer patients.
Primary end point: Complete response to treatment (CR; defined as no emesis and no use of rescue medications):

1) In the overall phase (OP; 0-120 hrs of chemotherapy),
2) In the acute phase (AP; 0-24 hrs), and
3) In the delayed phase (DP; 24-120 hrs).
• In addition to CR, we also assessed control of nausea in each phase, use of rescue medications in each phase and toxicity profile (TP).
• Stouffer's Z-score method used to test for overall effect.
16 Trials (n=5,547)

11 Trials (n=3,314)
Highly Emetogenic Chemotherapy

5 Trials (n=2,233)
Moderately Emetogenic Chemotherapy
Phase-wise changes in response with addition of Aprepitant to SAT

- Overall phase
  - SAT only: X
  - SAT + Aprepitant: Y
  - p-value < 0.0001

- Acute phase
  - SAT only: 70
  - SAT + Aprepitant: 82
  - p-value = 0.002

- Delayed phase
  - SAT only: 50
  - SAT + Aprepitant: 60
  - p-value < 0.0001
Control of nausea with addition of Aprepitant to SAT

Overall phase
Acute phase
Delayed phase

SAT only
SAT + Aprepitant

0.088
0.342
0.033
Rescue medications use with addition of Aprepitant to SAT

Overall phase
Acute phase
Delayed phase

SAT only  SAT + Aprepitant
Table 2: Toxicity data with addition of Aprepitant (A) to SAT

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Arm</th>
<th>Sample size</th>
<th>Event rate(%)</th>
<th>Odds Ratio</th>
<th>LCI</th>
<th>UCI</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>One or more clinical AE</td>
<td>SAT only</td>
<td>1255</td>
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<td>1.25</td>
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Conclusion

• ACR is effective in CINV due to both HEC and MEC in adult cancer patients.
• ACR improves the complete response (control of emesis without any rescue therapy) in all phases.
• ACR improves nausea only in delayed phase.
• Overall toxicity profile of Aprepitant Combination Regimens are similar to Standard antiemetic treatment. (except fatigue, hiccups, neutropenia).
• Aprepitant Combination Regimens cause more fatigue & hiccups, and lesser neutropenia.
• Addition of Aprepitant to SAT should routinely be done in patients undergoing highly or moderately emetogenic chemotherapy.
Future research considerations

- Exploring ACR in treatment of CINV, in addition to prevention of CINV.
- Exploring other Neurokinin-1 antagonist like casopitant in prevention and treatment of CINV.
References

Thank you

Dr. Gupta
Dr. Srivastava
Dr. Qazi
Dr. Woodman