Medication Management and Potential Drug Interactions During Mavacamten Therapy in Obstructive Hypertrophic Cardiomyopathy

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Introduction

- Hypertrophic cardiomyopathy is one of the most common inherited cardiac disorder impacting 1 in 500 adults in united states; with majority of adults with HCM have the obstructive symptoms at rest or with provocation[1]
- Historically, guideline-directed medication therapy consisted of mainly symptom relief.[1]
- Mavacamten is the first FDA-approved cardiac myosin inhibitor in the treatment of obstructive hypertrophic cardiomyopathy (oHCM) by improving left ventricular outflow tract (LVOT) obstruction and symptoms.[1,2]
- Mavacamten is a high risk medication and requires REMS due to systolic dysfunction risk[2]
- Mavacamten is primarily metabolized by CYP2C19 and to lesser extent CYP3A4
- Concomitant medications may alter drug exposure, making medication review and identification of potential drug-drug interactions important for safer therapy management in clinical practice.[1]

Objectives

To describe dosing patterns, concomitant CYP-interaction medications and adverse effects among adults with obstructive HCM treated with mavacamten at a single center.

Methods

Study Design:

- Single-center, hybrid prospective and retrospective observational study at USF Health

Inclusion Criteria:

- Adults ≥18 years with a confirmed diagnosis of oHCM
- Currently receiving, previously received or initiating mavacamten

Data Collection:

- Data abstraction was collected to from electronic health recorded included:
  - Demographics, mavacamten dosing, echocardiographic data including left ventricular ejection fraction (LVEF) and left ventricular outflow tract (LVOT), NYHA class, adverse events, and concomitant medications for each visit.

Analysis:

- Data were summarized using descrptive statistics; the limite dnumber of outcome event precluded inferential bivariate or multivariable analysis. Findings are reported descriptively due to the ongoing data abstraction

Process of Drug-Drug Interaction Assessment:

- Home medication list were reviewed and screened for known drug-drug interactions with mavacamten.
- Examples:
  - **Strong CYP2C19 Inhibitors**: Fluconazole, Fluvoxamine
  - **Moderate CYP2C19 Inhibitors**: Fluoxetine
  - **Weak CYP2C19 Inhibitors**: Omeprazole, esomeprazole
  - **Strong CYP3A4 Inhibitors**: Azoles

Results

Table 1: Sample Characteristic (n=43)

Age at mavacamten start, years	Mean ± SD	58.1 ± 14.4
	Median [IQR]	58.4 [51.8–68.8]
	Range	20.7–87.5
Sex, n (%)	Female	25 (58.1%)
	Male	18 (41.9%)
Race, n (%)	White	35 (83.3%)
	Black or African American	7 (16.7%)
Ethnicity, n (%)	Hispanic or Latino	6 (14.0%)
	Not Hispanic or Latino	37 (86.0%)

Dose Initiation and Dose Alterations

- Two patients initiated mavacamten at a dose lower than the standard starting dose due to a concomitant drug-drug interaction with fluoxetine.
- Dose alteration, defined as dose reduction, temporary hold, or discontinuation and excluding up-titration, occurred in 13 of 43 patients (30.2%).
- Among patients with dose alterations, 2 patients had a concomitant interacting medication; both required temporary mavacamten holds while receiving verapamil or diltiazem.
- The remaining 11 patients with dose alterations did not have an identified concomitant drug-drug interaction.
- No dose alterations were attributed to a drug-drug interaction.

Treatment Discontinuation and Adverse Effects

- Six patients discontinued mavacamten during follow-up.
- Among patients who discontinued mavacamten, 2 had a concomitant drug-drug interaction with diltiazem; neither discontinuation was attributed to LVEF reduction or LVOT gradient response.
- One patient had a follow-up LVEF below 50%; this patient did not have an identified concomitant drug-drug interaction.

Discussion

- Concomitant CYP-interacting medications were observed in roughly one-third of patients, most commonly calcium channel blockers (verapamil, diltiazem).
- Dose alterations were documented in about one-third of patients; none were recorded as attributable to a drug-drug interaction
- A small number of interaction-related dosing decisions were observed (reduced initial dose with fluoxetine; temporary holds with verapamil or diltiazem).
- These preliminary, descriptive observations are limited by sample size and ongoing data abstraction; no associations or conclusions can be drawn at this time.

Limitations:

- Small sample size limits statistical power and precludes meaningful inferential analysis
- Single-center, retrospective design limits generalizability
- CYP2C19 genotype was not assessed in this study; genotyping is not currently routine standard of care, yet metabolizer status is a key determinant of mavacamten exposure and may influence dosing and response

Future Direction

- Expand the cohort by enrolling additional patients to improve statistical power
- Incorporate CYP2C19 genotyping to characterize metabolizer status and evaluate its relationship to mavacamten dosing, response, and tolerability

References

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