1. ABSTRACT

- **Title**

Risk factors and incidence of inpatient constipation among migraine patients treated with erenumab: A retrospective cohort study in a US Electronic Health Record Database

Date: 23 March 2021

- **Keywords**

Constipation, erenumab, monoclonal antibodies, migraine, risk factors

- **Rationale and Background**

On 17 May 2018, erenumab-aooe (Aimovig®) became the first monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) pathway to be approved for the prevention of migraine in adults by the United States (US) Food and Drug Administration (FDA). In the three pivotal erenumab clinical trials, the incidence of constipation during the 12-week double-blinded treatment phase was 1% with placebo, 1% with the 70 mg erenumab dose, and 3% with the 140 mg dose. In October 2019, an update of constipation with serious complications was added to the Warning and Precautions section of the product label.

- **Research Question and Objectives**

The objectives of this study were:

1. To describe risk factors of inpatient constipation among migraine patients treated with erenumab
2. To estimate the 90-day incidence proportion of inpatient constipation among migraine patients treated with erenumab

- **Study Design**

Retrospective observational cohort study.

- **Setting**

US patients identified in the Optum Electronic Health Record (EHR) database.

- **Subjects and Study Size, Including Dropouts**

The study population included new users of erenumab identified from 17 May 2018 through 31 March 2019 in the Optum EHR database. The index date was the earliest date meeting all cohort eligibility criteria, which included:

- Had a prescription order for erenumab during the accrual period; only the first identified prescription order was considered
- Age ≥ 18 years
- Had at least 1 migraine diagnosis (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] G43.-) or prescription for a triptan/ergotamine in the 12 months prior to the erenumab prescription
- Had at least 1 outpatient (OP) visit at least 1 year prior to the erenumab prescription to establish the 12-month baseline period
- Had no use of any monoclonal antibodies targeting the CGRP pathway in the one year prior to the erenumab prescription

A total of 9994 patients met all eligibility criteria.

The baseline period for assessing patient characteristics was the 12-month period before the index date (inclusive of the index date).

- **Variables and Data Sources**

This study utilized the Optum EHR database, which is a de-identified patient-level database that integrates multiple electronic medical record data systems with medical claims, prescription, and practice management data.

Outcome variable: Inpatient constipation was defined using ICD-10-CM diagnosis codes for constipation in an emergency department (ED) or inpatient (IP) hospital setting only. Any constipation event occurring in either of these settings was counted, regardless of the primary reason for the visit. Among patients with inpatient constipation, the presence of serious complications was also captured and described as the presence of at least one ICD-10-CM diagnosis code for fecal impaction, intestinal obstructions, anal fissures and/or fistulas as well as other symptoms identified in an emergency department or inpatient hospital setting within 30 days following the date of the inpatient constipation event.

Exposure variable: Exposure was identified by National Drug Codes (NDC) for erenumab, as recorded in the prescription order table within the EHR database.

Covariates: We evaluated the following types of variables during the baseline period: demographics, and *a priori* defined covariates of interest, including comorbidities, concomitant medications, and risk factors for the outcome.

- **Results**

The majority of migraine patients were female (87.4%) and 40.6% were between 35 and 49 years of age. Chronic pain (50.8%), non-migraine headache (46.6%), and anxiety (35.1%) were the most common comorbidities. During the baseline period, 6.4% of erenumab initiators had a history of any constipation in any health care setting, 1.8% had a history of inpatient constipation, and 0.5% had a history of complications of inpatient constipation. Drugs that may cause constipation were also frequently prescribed during the baseline period including 56.5% of patients who used anticholinergics, 55.1% who used NSAIDs (either prescription or over-the-counter [OTC]), and 48.0% who used opioids.

Fifty-five inpatient constipation events were identified during the follow-up period, for an overall 90-day incidence proportion of 0.55% (95% confidence interval [CI]: 0.42–0.72%). The incidence was 0.58% (95% CI: 0.44–0.77%) in females and 0.32% (95% CI: 0.12–0.81%) in males. Compared to other age groups, the incidence of inpatient constipation was highest among patients ≥ 65 years of age (1.04%; 95% CI: 0.53–2.03%). Among patients who had a history of any constipation in any care setting during the baseline period, the incidence of inpatient constipation was 3.13% (95% CI: 2.04–4.79%), while the incidence was higher (6.63%; 95% CI: 3.83–11.23%) among those with a history of inpatient constipation. For individuals with a history of complications related to inpatient constipation, the incidence of inpatient constipation during the follow-up period was 11.54% (95% CI: 5.40–22.97%). The incidence of inpatient constipation was also higher among patients with other baseline risk factors (range: 0.62% - 4.11%) relative to the overall sample. Among patients with prescription orders for opioids, NSAIDs, and anticholinergics, the incidence proportions were 0.96% (95% CI: 0.72–1.28%), 0.80% (95% CI: 0.60–1.07%), and 0.78% (95% CI: 0.58–1.04%), respectively. At least 80% of the 55 patients who experienced inpatient constipation events had at least one prescription order for one of these 3 classes of medications during the baseline period. Of the 55 patients with inpatient constipation events, 6 had a serious complication within 30 days following the date of the inpatient constipation event.

- **Discussion**

In this study, the 90-day incidence proportion of inpatient constipation among new users of erenumab was 0.55%, which is similar to previously published findings among all migraine patients. The incidence proportion was higher in patients ≥65 years and among patients with pre-existing risks factors. The proportion of patients with prescription orders for other medications (eg, anticholinergics, NSAIDs, opioids) that may cause constipation was high in this study population. Further research on the incidence of inpatient constipation in non-erenumab users with migraine will help contextualize the findings of the present study. The findings in this study were descriptive in nature and were not intended for causal inference; therefore, there is no impact on the benefit-risk profile of erenumab.

- **Marketing Authorization Holder(s)**

Amgen, Inc.

- **Names and Affiliations of Principal Investigator**

[redacted] Center for Observational Research, Amgen, Inc.

2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence Interval
EHR	Electronic Health Record
ED	Emergency Department
FDA	Food and Drug Administration
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IP	Inpatient
NDC	National Drug Code
OP	Outpatient
OTC	Over-The-Counter
SOP	Standard Operating Procedure
US	United States