Title: Risk Factors and Incidence of Inpatient Constipation and Inpatient Constipation With Serious Complications Among Migraine Patients Treated With Erenumab: A Retrospective Cohort Study in a US Electronic Health Record Database

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1. BACKGROUND AND RATIONALE

Migraine is a neurological disorder characterized by recurrent headache attacks of moderate to severe pain, affecting up to 18% of the female population and 6% of the male population (Katsarava et al, 2012). The incidence of constipation was 1% with placebo, 1% with 70 mg, and 3% with 140 mg in the three erenumab pivotal clinical trials during the 12-week double-blinded treatment phase (Dodick et al, 2018; Erenumab Prescribing Information, March 2019; Goadsby et al, 2017; Tepper et al, 2017). In October 2019, an update of constipation with serious complications was added to the Warning and Precautions section of the product label. As such, this retrospective observational study will describe the incidence and risk factors for inpatient constipation and inpatient constipation with serious complications among migraine patients treated with erenumab to give context to events observed in the clinical trials as well as real-world observations from post-marketing surveillance data.

2. OBJECTIVES

1. To describe risk factors of inpatient constipation and inpatient constipation with serious complications among migraine patients treated with erenumab.
2. To estimate the cumulative incidence proportion of inpatient constipation and inpatient constipation with serious complications among migraine patients treated with erenumab.

3. STUDY POPULATION/SAMPLE SIZE/STATISTICAL ANALYSES PLANS

A retrospective cohort study will be conducted using the Optum's Electronic Health Record (EHR) Research Database. The Optum EHR database is a de-identified patient-level database that integrates multiple electronic medical record data systems with medical claims, prescription, and practice management data. The Optum EHR database has information on erenumab prescriptions from the free drug program, therefore reducing the potential for misclassification of exposure at the start of erenumab treatment, particularly in light of the fact that constipation is expected to occur shortly after initiation of treatment. Additionally, the Optum EHR database will allow for more complete ascertainment of personal and family history of constipation, which are risk factors for serious constipation events.

Study population / inclusion criteria

The study population will include patients with a migraine diagnosis on or prior to receiving a prescription order for erenumab identified from 17 May 2018 through

30 June 2019 (or latest available data). Patients receiving erenumab will be identified using National Drug Codes (NDC) as recorded in the prescription order table within the EHR database. Migraine patients will be identified using a combination of ICD-10-CM migraine diagnosis codes (G43.-) and acute migraine-specific medication (triptans or ergots). To be included, patients must be at least 18 years or older at the time of the erenumab prescription order and have at least one outpatient clinical visit at least one year prior to the index date to establish baseline medications, risk factors, and patient characteristics. The minimum time requirement for establishing baseline factors may change due to sample size considerations. We will examine the number of patients who have a visit at least 6, 9, and 12 months prior to their index date. The index date will be defined as the date of the earliest prescription order for erenumab that meets all these criteria.

Inpatient constipation events / outcome assessment

Inpatient constipation will be defined using ICD-10-CM diagnosis codes for constipation in an emergency room or inpatient hospital setting only. Appendix A lists the ICD-10-CM codes used for constipation events. Among patients with inpatient constipation, the presence of serious complications will be described by 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 room or inpatient hospital setting. Appendix B lists the ICD-10-CM codes used for identification of serious complications. Follow-up for inpatient constipation will start the day after index date until earliest of 1) a prescription for another CGRP antagonist (galcanezumab or fremanezumab), 2) the end of the study period, or 3) occurrence of the inpatient constipation event of interest. We will also consider implementing a minimum time of follow-up availability by assessing the number of patients that would be excluded when implementing a minimum 30-day, 60-day, or 90-day time until end of follow-up as described above. We will conduct sensitivity analyses to understand mean/median time of follow-up using date of last visit as a proxy for end of follow-up.

Constipation events not identified in a setting other than emergency room or inpatient hospital setting (ie, diagnoses for constipation in an outpatient setting) will not be assessed as an outcome. However, occurrence of any constipation (identified during an outpatient, ER, or inpatient encounter) will be described during the baseline period in all migraine patients who initiate erenumab in the study period.

Demographic variables, covariates, and risk factors

The study cohort will be described with respect to underlying risk factors for constipation documented during the baseline period, up to and including the index date. The full list of demographic variables, covariates, and risk factors is detailed in Appendix C and is subject to further refinement as the study progresses. Comorbidities will be identified using ICD-10-CM diagnosis codes from the structured EHR diagnosis tables and medications will be identified using NDCs recorded on prescription order tables of the EHR database. Characteristics which are not fully ascertained from the EHR diagnosis tables (eg, personal and family history of constipation) will be ascertained through examination of semi-structured data derived from the natural language processing (NLP) table. The occurrence of inpatient constipation in the follow-up period will be stratified by presence/absence of documented any constipation in the baseline period.

Sample size and statistical analysis plans

A total of 18,941 patients with a prescription order for erenumab were identified within the Optum EHR database from May 2018 through June 2019. Table 1 provides the 95% confidence interval estimates for various rates of constipation (0.5%, 1%, 3%, 5%, 10%, and 20%) based on a starting sample of 18,941 erenumab initiators.

Table 1. 95% Confidence Interval Estimates (and half-widths) for a Range of Constipation Values, Based on Overall 18,941 Erenumab Initiators

Constipation (%)	95% CI	Half-Width of CI
0.50	0.40 – 0.60	0.10
1.00	0.86 – 1.14	0.14
3.00	2.76 – 3.24	0.24
5.00	4.69 – 5.31	0.31
10.00	9.57 – 10.43	0.43
20.00	19.43 – 20.57	0.57

Although the final sample size for the study will change due to the criteria applied during the conduct of the protocol, we expect to be able to detect high cumulative incidence proportions of serious constipation with a small margin of error, even if there are reductions in sample size due to the implementation of the cohort entry criteria.

For the analysis, the risk of inpatient constipation (and the subset with serious complications) among the erenumab cohort will be described overall and stratified by the presence/absence of gastrointestinal conditions or other comorbidities in the baseline

period. The erenumab cohort will be described by frequencies and percentages according to demographics and other baseline risk factors. Counts of inpatient constipation events (and the subset with serious complications) observed starting from the day after the index date through the end of the study period (or switching to another anti-CGRP medication) will be tabulated. Only the earliest (first observed) inpatient constipation event will be counted. The cumulative incidence proportion of inpatient constipation (and the subset with serious complications) will be calculated as the number of events identified during follow-up divided by the number of patients at risk for the event (along with 95% confidence intervals).

Limitations

As is true for most clinical record-keeping systems, Optum's EHR data do not include systematic information about enrollment and is based on information collected during clinical encounters (eg, outpatient physician visits, ER visit, inpatient hospital stays). Loss to follow-up therefore cannot be directly determined and we do not know exactly when patients are at risk for developing events (we do, however, have visit dates to determine when events of interest occurred). Due to the relatively short study period, we expect bias due to loss to follow-up in this study to be minimal. Additionally, the calculation of cumulative incidence proportion, which is calculated using the number of patients at risk as the denominator, is less susceptible to bias due to loss of follow-up as compared to the calculation of incidence rates, which is calculated using person-time at risk as the denominator.

Although we can assess documentation of prescriptions in the system, we cannot assess whether those prescriptions were filled or taken by the patient. Similarly, given the nature of the EHR data, we may underestimate the presence of some risk factors.

4. COLLECTION, RECORDING, AND REPORTING OF SAFETY INFORMATION AND PRODUCT COMPLAINTS

4.1 Safety Collection and Recording Requirements

This study is analyzing secondary data from the Optum Electronic Health Record Research Database. The safety outcomes that are listed in section 3 (constipation events/outcome assessment) will be documented and analyzed in this study. These will be reported in aggregate in the final study report as rates. See section 3 Constipation events/outcome assessment for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety events

suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

5. PATIENT CONFIDENTIALITY

This study will comply with all applicable laws regarding patient privacy. No direct patient contact or collection of additional patient data will occur. Study results will be in tabular form and aggregate analyses that omits patient identification. Any publications and reports will not include patient identifiers.

6. PUBLICATION INTENT

The results of this study will be submitted for publication. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The contractual agreement between the institution, Investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

7. REFERENCES

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8. APPENDICES

Appendix A. Constipation Codes

Code	Code type	Code description	Setting
K59.0	ICD-10-CM Diagnosis	Constipation	1 IP / 1 ER
K59.00	ICD-10-CM Diagnosis	Constipation, unspecified	1 IP / 1 ER
K59.01	ICD-10-CM Diagnosis	Slow transit constipation	1 IP / 1 ER
K59.02	ICD-10-CM Diagnosis	Outlet dysfunction constipation	1 IP / 1 ER
K59.03	ICD-10-CM Diagnosis	Drug induced constipation	1 IP / 1 ER
K59.04	ICD-10-CM Diagnosis	Chronic idiopathic constipation	1 IP / 1 ER
K59.09	ICD-10-CM Diagnosis	Other constipation	1 IP / 1 ER

Appendix B. Complications of Constipation Codes

Code	Code type	Code description	Setting
K56.41	ICD-10-CM Diagnosis	Fecal impaction	1 IP / 1 ER
K56.49	ICD-10-CM Diagnosis	Other impaction of intestine	1 IP / 1 ER
K56.60	ICD-10-CM Diagnosis	Unspecified intestinal obstruction	1 IP / 1 ER
K56.600	ICD-10-CM Diagnosis	Partial intestinal obstruction, unspecified as to cause	1 IP / 1 ER
K56.601	ICD-10-CM Diagnosis	Complete intestinal obstruction, unspecified as to cause	1 IP / 1 ER
K56.609	ICD-10-CM Diagnosis	Unspecified intestinal obstruction, unspecified as to partial versus complete obstruction	1 IP / 1 ER
K59.39	ICD-10-CM Diagnosis	Other megacolon	1 IP / 1 ER
K62.2	ICD-10-CM Diagnosis	Anal prolapse	1 IP / 1 ER
K62.3	ICD-10-CM Diagnosis	Rectal prolapse	1 IP / 1 ER
K60.2	ICD-10-CM Diagnosis	Anal fissure, unspecified	1 IP / 1 ER
K60.3	ICD-10-CM Diagnosis	Anal fistula	1 IP / 1 ER
K60.4	ICD-10-CM Diagnosis	Rectal fistula	1 IP / 1 ER
K60.5	ICD-10-CM Diagnosis	Anorectal fistula	1 IP / 1 ER
K62.6	ICD-10-CM Diagnosis	Ulcer of anus and rectum	1 IP / 1 ER
K56.0	ICD-10-CM Diagnosis	Paralytic ileus	1 IP / 1 ER
K56.7	ICD-10-CM Diagnosis	Ileus, unspecified	1 IP / 1 ER

Appendix C. Table of Demographic Variables, Covariates, and Risk Factors*

Demographics:
- Age, gender, body mass index, socioeconomic status, and geographic region

Migraine preventive agents:
- CGRP-receptor antagonists
- Migraine preventive anti-hypertensives
- Migraine preventive anti-epileptics
- Migraine preventive anti-depressants
- Botulinum-toxins
- Other migraine preventives

Comorbidities related to migraine:
- Asthma
- Hypertension
- Anxiety
- Depression
- Non-migraine headache
- Chronic pain
- Insomnia
- Thyroid disorder

Prescription drugs related to constipation:
- Prescription drugs that may cause constipation
  - Opioids
  - Anticholinergics (antipsychotics, antihistamines, antispasmodics, antiparkinsonian drugs, tricyclic antidepressants)
  - NSAIDs
- Prescription drugs that treat constipation
  - Prescription laxatives (lactulose)
  - Other prescription treatments (tegaserod, linaclotides, lubiprostone)

Potential medical risk factors for constipation:
- Gastrointestinal disorders
  - Irritable bowel syndrome
  - Crohn's disease
  - Ulcerative colitis
  - Diverticulitis/diverticulosis
  - Hemorrhoids (excluding pregnancy-induced)
- Disorders that are associated with constipation
  - Diabetes mellitus
  - Autonomic neuropathy
  - Multiple sclerosis

Constipation or complications of constipation:

- Any constipation (OP/IP/ER)
- Constipation (IP/ER)
- Complications of constipation (IP/ER)
  - Fecal impaction
  - Impaction of intestine
  - Bowel perforation
  - Bowel/intestinal obstruction
  - Megacolon
  - Rectal prolapse
  - Anal fissure
  - Anal fistula
  - Ulcer of anus and rectum
  - Paralytic ileus
  - Removal of impacted feces

- ** These are examples of the types of factors to be included but others may be added and some may be removed*