Risk of Hypertension in Erenumab-treated Patients with Migraine in Clinical Trials and in the Postmarketing Setting

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Introduction

- Erenumab (in the US, erenumab-aooe), a monoclonal antibody (mAb) targeting the canonical calcitonin gene-related peptide (CGRP) receptor, was approved in the US for the preventive treatment of migraine in adults in 2018[1]
- Because CGRP dilates blood vessels, hypertension has been a theoretical risk during the developmental programs for erenumab and other therapies that target CGRP or its receptor[2]
- While no evidence of an association between erenumab treatment and vascular events was observed during the clinical development program,[3] hypertension adverse events (AEs) have been reported following the use of erenumab in the postmarketing setting[1]
- In April 2020, the US Prescribing Information for erenumab was updated to include the risk of hypertension based on postmarketing experience[1]
- More extensive clinical trial, real-world evidence, and postmarketing surveillance is needed to assess the risk of hypertension among migraine patients treated with CGRP-pathway mAbs and small molecule receptor antagonists

Objective

To assess the risk of hypertension among migraine patients treated with erenumab in clinical trials and in the postmarketing setting

Methods

- Hypertension AEs were identified from the Amgen Clinical Trial and Global Safety Databases using the standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for hypertension (broad search terms); all cases identified using this strategy were included in the analysis, including reports that contained limited information and those that described an alternative etiology for the development of hypertension

Clinical Trials

- Safety data from four phase 2/3 studies were used to perform a pooled analysis of migraine patients ≥ 18 and ≤ 60 or 65 years of age[3]
- Cardiovascular exclusion criteria and frequency of blood pressure (BP) monitoring for each study are described in Table 1. BP data for each patient were based on the average of at least two measurements (separated by at least 5 minutes) and were obtained after the patient had been in a semi-recumbent or supine position in a rested state for at least 5 minutes. The position used for each patient was consistently used for each measurement throughout the study

Postmarketing

- Time period for analysis of postmarketing adverse event reports: May 17, 2018–January 31, 2020

Table 1: Clinical Trial Exclusion Criteria and BP Collection Frequency for Erenumab

ClinicalTrials.gov Identifier	Cardiovascular Exclusion Criteria	Timepoints for BP Collection
NCT01952574*	Poorly controlled hypertension (systolic BP ≥ 150 mmHg and/or diastolic BP ≥ 90 mmHg)	Every 2-4 weeks of 12-week DBTP; every 4 weeks through week 64 of OLTP then every 12 weeks for weeks 76–256
NCT02066415†	Poorly controlled hypertension in the judgement of the investigator ***or*** systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg	Every 2-4 weeks of 12-week DBTP; every 4 weeks during 13-month OLTP
NCT02456740*	None for BP	Every 4 weeks of 24-week DBTP and 28-week ATP
NCT02483585*	None for BP	Every 4 weeks of 12-week DBTP and 28-week OLTP
All Studies	Myocardial infarction, stroke, TIA, unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening	

*EM studies. †CM studies. ATP, active treatment phase; BP, blood pressure; CM, chronic migraine; DBTP, double-blind treatment phase; EM, episodic migraine; OLTP, open-label treatment phase; TIA, transient ischemic attack.

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Results

Clinical Trials

- During the 12-week, double-blind, placebo-controlled, treatment phase (DBTP) across the pooled studies, the incidence of hypertension AEs and proportion of patients initiating antihypertensive medication were similar across treatment groups (Table 2)
- In a long-term study of open-label erenumab treatment for up to 5 years,[4] the incidence of hypertension did not increase over time (exposure-adjusted incidence of hypertension was 1.9 per 100 patient-years for erenumab 70/140 mg)

Postmarketing

- In the postmarketing setting (245,682 person-years exposure through January 31, 2020), 362 hypertension AEs (355 cases; 0.144 per 100 person-years) were reported (Table 3)
  - Most of the reported AEs were non-serious (73.8%)
  - There was an approximately equal distribution of solicited events (47.0%) and spontaneous reports (53.0%)
  - Almost half of the events were medically confirmed (46.1%)
  - A total of 123 (34.0%) AEs were from a non-US region

Table 2: 12-Week DBTP Pooled Analysis Results

	Placebo (N = 1043)	Erenumab 70 mg (N = 893)	Erenumab 140 mg (N = 507)
Incidence of hypertension AEs, n (%)	9 (0.9)	7 (0.8)	1 (0.2)
Exposure-adjusted incidence rates of hypertension, per 100 patient-years	3.6	3.3	0.8
Patients without antihypertensive medication at baseline, n	972	859	485
Patients initiating antihypertensive medication* during 12-week DBTP, n (%†)	12 (1.2)	7 (0.8)	1 (0.2)

N = number of patients in the analysis set. *Antihypertensive medications with a reported indication of hypertension. †Percentage calculated based on number of patients without antihypertensive medication at baseline.
AEs, adverse events; DBTP, double-blind treatment phase.

Table 3: Characteristics of Postmarketing Adverse Events

	AEs, n (%)
Seriousness*	
Serious	95 (26.2)
Non-serious	267 (73.8)
Report Type	
Solicited	170 (47.0)
Spontaneous	192 (53.0)
Country of Report	
United States	239 (66.0)
Non-United States region	123 (34.0)

*Hypertension AEs were designated as serious if they resulted in death, were life-threatening, required hospitalization, resulted in disability, and/or were deemed medically significant.

Table 4: Patient Demographics

Patient Demographics	N = 355 Cases
Gender, n (%)	
Female	261 (73.5)
Male	45 (12.7)
Unknown	49 (13.8)
Age*	
Mean, years	53.1
Median, years	53
Range, years	24–87
Age group*, years, n (%)	
24–30	12 (4.8)
31–40	25 (9.9)
41–50	58 (23.0)
51–60	80 (31.7)
61–70	55 (21.8)
71–80	17 (6.7)
81–87	5 (2.0)

*Based on data available for 252 cases.

Table 5. Characteristics of Serious and Nonserious Hypertension AEs	Serious AEs (N = 95), n (%)	Nonserious AEs (N = 267), n (%)
Risk factors*		
Previous documented hypertension	32 (33.7)	30 (11.2)
Diabetes	5 (5.3)	8 (3.0)
Cardiovascular disease	4 (4.2)	3 (1.1)
Obstructive sleep apnea	2 (2.1)	1 (0.04)
Obesity	5 (5.3)	5 (1.9)
Thyroid disease	7 (7.4)	6 (2.3)
Triptan or ergot alkaloid use for acute migraine exacerbation	8 (8.4)	10 (3.7)
Acute elevation of BP associated with migraine pain	4 (4.2)	78 (29.2)
Prior history of preeclampsia in earlier pregnancy†	1 (1.1)	0 (0)
Documented smoker	1 (1.1)	6 (2.3)
Unknown/undocumented	51 (53.7)	153 (57.3)
Time to onset		
≤1 day	11 (11.6)	32 (12.0)
>1 day to ≤1 week	9 (9.5)	4 (1.5)
>1 week to ≤2 weeks	5 (5.3)	9 (3.4)
>2 weeks to ≤1 month	6 (6.3)	8 (3.0)
>1 month to ≤2 months	4 (4.2)	7 (2.6)
>2 months to ≤3 months	6 (6.3)	2 (0.7)
>3 months	5 (5.3)	13 (4.9)
Unknown	49 (51.6)	192 (71.9)
Action taken with erenumab at the time of report		
Discontinued	36 (37.9)	70 (26.2)
No change	13 (13.7)	51 (19.1)
Temporarily withheld	1 (1.1)	4 (1.5)
Dose decreased	0 (0)	3 (1.1)
Dose increased	2 (2.1)	5 (1.9)
Unknown	43 (45.2)	134 (50.2)
Number of elevated BP measures documented:		
1	80 (84.2)	252 (94.4)
2	12 (12.6)	9 (3.4)
3	2 (2.1)	1 (0.4)
4	1 (1.1)	5 (1.9)
Treatment for the hypertension event:		
No treatment documented	75 (78.9)	246 (92.1)
Restarted or changed previously discontinued anti-HTN meds	10 (10.6)	5 (1.9)
Started new anti-HTN meds	10 (10.5)	16 (6.0)

*Some hypertension AEs were associated with > 1 risk factor. †1 event of preeclampsia in a 37 year old female who had similar issues in a previous pregnancy (prior to erenumab).
AEs, adverse events; BP, blood pressure; HTN, hypertension.

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Conclusions

- Clinical trials did not demonstrate an increased risk of hypertension in patients with migraine treated with erenumab compared with placebo
- In the postmarketing setting, using the Amgen Global Safety Database, hypertension AEs have been reported following the use of erenumab, many of which occurred in patients who had pre-existing hypertension or risk factors for hypertension
- The majority of postmarketing cases did not describe the time to hypertension onset; of the cases with this information available, most occurred within one week of the first administration of erenumab
- Given the limitations of postmarketing AE reports (eg, incomplete information, lack of a control arm), additional data are needed to fully characterize the nature, timing, and extent to which hypertension is a risk associated with erenumab and other CGRP-pathway antagonists

Scan the QR code to access the corresponding infographic

Risk of Hypertension in Erenumab-treated Patients with Migraine in Clinical Trials and in the Postmarketing Setting

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Scan the QR code to access the Migraine Knowledge Center

Disclosures

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